

ELLIS HORWOOD PUBLISHERS

THE BIOCHEMICAL EFFECTS OF DRUGS IN PREGNANCY

VOLUME 2

diuretics, digestive
and pulmonary tract
drugs, hormones,
antihormones and
steroid hormones,
analgesics,
metabolic action
drugs,
antibiotics and
chemotherapeutic
substances,
vaccines and sera

A. ONNIS
and
P. GRELLA



Ellis Horwood Series

Biochemistry in Medicine and Pharmacology

Series Editor: Jackie de Belleruche, Lecturer in Neurochemistry, Charing Cross Hospital Medical School, London

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DRUGS IN PREGNANCY**

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**Diuretics, Digestive and Pulmonary Tract Drugs,
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Analgesics, Metabolic Action Drugs, Antibiotics
and Chemotherapeutic Substances, Vaccines and
Sera**

A. ONNIS, Professor of Clinical Obstetrics, and
Director of the Obstetric and Gynaecological
Clinic, University of Padua, and P. GRELLA,
Professor of Prenatal Paediatrics, University of
Padua

Translation Editor: PETER J. LEWIS, formerly Department of Clinical Pharmacology, Royal Postgraduate Medical School, now Director, Strasbourg Center, Merrell Dow Research Institute, France

Since the thalidomide disaster of the 1960's, the consequences of which are still being felt worldwide, the use of drugs both in pregnant and non-pregnant patients has been widely questioned and examined.

This book takes a logical approach to the problem, in a two-volume investigation of all currently-known drugs used on both human beings and on animals, gathering all presently-available information on drug safety, thereby assessing the risk-to-benefit ratio of all drugs likely to be prescribed to women during (and before) pregnancy. It covers a range of pharmaceutical products not available elsewhere in such comprehensive and yet easily-assimilable form not previously available. The biochemical effects of each drug are carefully annotated and explained, and the responses of the patient (and the foetus or neonate where possible) are charted.

The spectrum of drugs covered in these pages varies from those used for conditions *not* related to pregnancy (e.g. in cases where tranquillizers, anaesthetic drugs, and analgesics are required): to drugs prescribed for conditions directly related to the pregnancy (e.g. nausea, heartburn, hormones).

The value of this book to all those either producing or prescribing drugs which may be taken by the pregnant patient is unquestionable. It will inform those involved in drug manufacture and marketing, and become a worthy reference tool for the medical and related professions for many years to come.

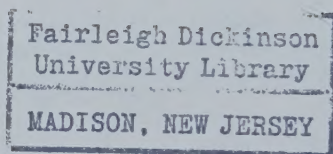
Readership: The pharmaceutical industry, world wide, whether directly or indirectly concerned with drugs that may be taken during pregnancy; biochemists, physicians, gynaecologists, obstetricians, clinicians, pathologists, paediatricians, neurologists, hospital and public health institutes, government health departments (for both human and veterinary aspects), veterinary and agricultural scientists (practising and researching), those concerned with cancer research, and the intelligent interested layman.

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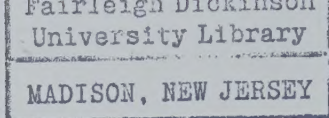
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Preface

Society has always striven to protect the pregnant woman. In ancient Greece and pharaonic Egypt special attention was paid to the diet, hygiene, and drug treatment of the expectant mother. The dangers of certain drugs in pregnancy were mentioned by Mauriceau in the second half of the 17th century. At the end of the 18th century the concept of birth malformations being due to 'divine anger' began to be replaced by more biological explanations. In the middle of the 19th century Da Reste [1] and others began research on experimental teratogenesis, and it was shown that some foetal malformations could be caused by chemicals.

Ancl (1933) [2] showed that chemical or physical agents could have a reproducible teratogenic effect in mammals and birds if applied at particular stages of development. However, concern about teratogenicity in human pregnancy is quite recent. In 1959 such possibilities were discussed [3], but it was the thalidomide disaster of 1960 which brought the subject to everyone's attention. Since that time the use of drugs in pregnancy has become a highly emotional issue. A logical approach to the problems of drugs in pregnancy is to gather information on drug safety in a systematic way, assessing the risk to benefit ratio for all drugs likely to be used in pregnant women. This is a mammoth task, but the present work is an attempt to do this in a comprehensive way.

In recent years, work on the teratogenicity of drugs has noticeably increased, but so far as the practising doctor is concerned the literature is not helpful. Package inserts which state 'To be used with caution in pregnancy' do not contain enough specific information to be useful.

In publishing this book we hope to provide more precise, more useful and more complete data. We hope that clinicians will respond by contributing their own experiences or drawing our attention to literature we have overlooked. In this way future editions may, we hope, be improved.

A. ONNIS

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The publishers are indebted to Monique Maxwell for her help with the proof reading and indexing of this work.

PUBLISHERS' NOTE

Since the safety of drugs and their administration to both pregnant and non-pregnant patients is constantly under medical and scientific review, it is always wise to check the most recent literature when prescribing drugs discussed in this book. Drugs quoted in the text are not necessarily in line with normal therapeutic drug doses prescribed to patients, as in most cases drugs in this book were prescribed on a purely experimental basis.

Introduction

There is no doubt that over-prescribing of drugs is a major problem in modern medicine, and nowhere is unnecessary use of drugs more dangerous than in pregnancy. On the other hand, modern drugs have made a major contribution to human health, and even in pregnancy drugs still play an important part in treating maternal diseases and in relieving pain in labour.

In an ideal world no medical treatment would be required in pregnancy, but the reality is that many women develop conditions requiring treatment when they are pregnant. An absolute ban on drug usage in pregnancy would not be practical, and in any case would be as logical a response to the thalidomide disaster as abolishing air travel after a single aircraft crash.

Unfortunately, not all responses to disasters are logical, and in the case of drugs in pregnancy some of the responses are not medical. The issue has become one of public policy and legal responsibility, and it even has a political dimension.

In this complex situation the prescribing doctor finds himself in difficulty. He is perhaps not well read in the science of teratogenicity, but he knows that the patient is half informed about the risk of drugs in pregnancy and will blame any adverse event in the pregnancy on the drugs which he prescribes.

In such a situation the doctor should be able to talk knowledgeably to the patient of risks and benefits for the drug concerned. It has been our aim to supply the information he requires. The present book is certainly not infallible, and no doubt some recommendations will change in the future as a result of new information. It is, however, as complete as we are able to make it. If there are errors or omissions we would be grateful to hear of them.

EFFECTS OF DRUGS ON THE FOETUS

The effects of drugs given to pregnant women, the embryo, or foetus are difficult to predict. A summary of the main considerations as to the effects of drugs on the products of conception will now be given, leaving a more detailed consideration for later [1, 2, 3, 4].

Maternal pharmacokinetics and pharmacodynamics

Large physiological changes occur in pregnancy. Maternal weight increases not only because of growth of the products of conception and expansion of the uterus but because of an increase in circulating blood volume and body water. There is an increase in oxygen consumption, in basal metabolism, cardiac output, and red cell mass; and there are changes in the distribution of cardiac output, with particular increases in uterine and renal blood flow. The resistance and tone of blood vessels all over the body are changed. There is a profound change in renal physiology; an increase in glomerular filtration rate and alterations in tubular function. This is not all, for there is a change in the metabolism of protein, lipids, and carbohydrates, and changes in electrolyte balance. The alterations that occur in plasma proteins could and do have an important bearing on the distribution of drugs, many of which are highly protein bound.

The alterations in coagulation factors have an obvious significance for the requirement of anticoagulants. In women who develop complications of pregnancy, such as diabetes, hypertension, and renal impairment, the situation is still more complicated.

Transplacental passage of drugs

The placenta is still widely thought of as being a barrier between the mother and the foetus. For the majority of drugs this is an erroneous concept. It is also worth remembering that prior to the development of the placenta some drugs will be present in the tubular and uterine secretions and in contact with the blastocyst even as it migrates towards the point of implantation. The mechanisms which regulate the transfer of drugs from mother to foetus are the following:

1. *Simple diffusion.* Most exogenous chemical substances, particularly those of low molecular weight, gain access to the foetus by diffusion. Of importance here are the concentration gradient, the area of exchange across the placenta, the structural characteristics of the placental tissue to be crossed, and the physicochemical nature of the drug itself. These last include the size and spatial conformation of the molecule, its degree of ionization, lipid solubility, and extent of binding to macroprotein molecules. Drugs which are undissociated and highly lipid soluble diffuse most rapidly.
2. *Facilitated diffusion.* Some substances pass more rapidly across the placenta because facilitatory mechanisms exist at the cellular membrane level. An example of this would be facilitated diffusion of iron.
3. *Active transport.* Some drugs are actively transported across the placenta by a process which uses metabolic energy. An example of this is the diuretic triamterene.
4. *Transport of metabolites.* Some drug molecules are transported into the foetus only after metabolic transformation. An example would be ascorbic acid.

5. *Direct transport.* Occasionally the maternal and foetal circulations are in direct contact, as evidenced by passage of foetal erythrocytes into the mother and vice versa. This is an infrequent occurrence, and it probably does not play any important role in the transfer of drugs.

Metabolic transformation of drugs in the placenta

Within the placenta drugs can be metabolized, and such metabolic transformation may make the drug either more or less biologically active. There are four fundamental processes of biotransformation: oxidation, reduction, hydrolysis, and conjugation. Hydroxylation is a particularly important example of oxidative metabolism, hydrogenation of double bonds is an important example of reduction while the breaking of amide and ester bonds are hydrolytic reactions. The formation of glucuronides and sulphates are examples of conjugation reactions.

Trophoblastic cells of the placenta contain an abundance of endoplasmic reticulum, the cellular organelle where microsomal enzymes which perform these functions are situated. In the placenta all these reactions take place. Phosphatases liberate energy-rich phosphate bonds, sulphatases participate in the synthesis of oestriol, amino oxidase and catechol-O-methyltransferase inactivate biogenic amines, and peptidases modify polypeptides such as angiotensin, oxytocin, and ADH.

The effects of drugs on placental function are of significance. Some drugs can enhance enzymic activity in the placenta by induction, and others can inhibit enzymic activities such as those involved in steroid metabolism, particularly processes of aromatization. Other drugs reduce the utilization of glucose by the placenta and can thus modify a principal energy substrate utilized by the foetus.

Distribution and transformation of drugs within the foetus

The distribution of drugs in foetal tissue has been studied in experimental animals by autoradiography following administration of a radioactive drug. The large amounts of data thus obtained in different animal species suggest that the distribution of drugs in the foetus is similar to that in the adult organism. However, there are differences, particularly in early pregnancy. The blood-brain barrier develops late in foetal life, so the distribution of drugs in the foetus shows some important differences from that in the adult.

Some examples of selectivity of uptake in different foetal organs which have practical significance are those of chloroquine fixing in the retina, of streptomycin and other aminoglycosides fixing in the acoustic nerve, and of iodine and antithyroid drugs being taken up by the thyroid. Tetracycline is concentrated in bone tissue and in dentine. Drug metabolizing enzymes within the foetus increase gradually as the foetus matures. Several studies have been done on human foetal tissue from legal abortions. In human foetal liver, there is a high capacity for oxidation of drugs, while reductive transformations and

reduction in transformation in hydrolytic processes are often depressed. In the first and second trimester, the foetal liver has a glucuronyl transferase activity less than one tenth that of the adult. In the adrenal glands oxidation and demethylation are poorly developed, while metabolism by reduction is similar to that in the adult. In general, drug metabolism in foetal tissue is less well developed than that in the adult, and hence the capacity to detoxify drugs is greatly reduced. This is important, particularly in the neonate and more particularly in premature neonates where drugs may be very slowly eliminated.

To reduce transplacental passage of drugs when labour is imminent, it is important to avoid

- (a) drugs which foetal enzyme systems are not efficient at coping with, such as those which must be glucuronidated;
- (b) drugs which might displace bilirubin from plasma protein;
- (c) drugs which may provoke physical dependence;
- (d) drugs which are potentially myelotoxic;
- (e) drugs which inhibit synthesis of prothrombin;
- (f) drugs which reduce haemolysis in G6PD deficient individuals, such as sulphonamides, phenacetin, chloramphenicol, nitrofurantoin, and aspirin.

Some ill effects of drugs in pregnancy are only apparent in the neonate. Among these effects are paralytic ileus caused by ganglion blockers, central depression caused by sedatives, cortico-adrenal suppression caused by the corticosteroids, hypothyroidism caused by antithyroid drugs, congestion of upper airways by reserpine, and haemorrhage caused by coumarin anticoagulants.

• Still other drugs may have a very long latency before they declare their ill effects. The most notable example is diethylstilboestrol, predisposing the female foetus to vaginal adenocarcinoma but only manifested in adolescence.

Teratogenic effects of drugs

Congenital malformations caused by drugs are much feared but are probably very infrequent. It has been estimated that 3% of all malformations are due to exogenous causes, such as infections, gamma radiation, and drugs. In fact, there are very few drugs which are able to produce malformation in human pregnancy. Such parameters as gestational age, type of drug, genetic background, dose, and time of administration are all important.

Gestational age

- (a) The blastocyst, prior to implantation, is relatively resistant to damaging agents, and it is commonly held that the blastocyst is either unharmed by the drug or killed by it.
- (b) During the period of organogenesis, from the third to tenth week of pregnancy, the type of malformation caused by a drug is critically dependent on gestational age. Each organ has a period of maximum sensitivity, generally

corresponding to the most rapid phase of development and the most intense differentiation. However, many organs develop simultaneously, and hence multiple malformations are possible.

- (c) After the first trimester most organs have already been formed, with the exception of the genital apparatus. This remains still sensitive to teratogenic agents. The central nervous system matures gradually in the latter half of pregnancy, and so psychotropic drugs and sex hormones are able to produce modifications of postnatal behaviour and of gonadotrophin secretion by an action late in pregnancy.

Nature of the drug

Some drugs are selectively taken up by the foetal organs and hence cause selective malformations. Examples are lesions of the acoustic nerve caused by streptomycin and lesions of the limbs caused by thalidomide.

Genetics of the foetus

The genetic background of the foetus is extremely important. It modifies the gravity, localization, and frequency of malformations.

Animal species differ in their response to teratogenic agents. Herein lies the problem of teratogenicity tests in animals and their non-applicability to man.

Dose and time of administration

Teratogenic effects are very dependent upon dose and on duration of administration. A single dose may be either more or less damaging than repeated doses because of such effects as enzyme induction.

Some drugs have an effect on the gametes, usually during gametogenesis. Drugs with mutagenic effects of this sort include cytotoxic drugs, cinchona alkaloids, and podophyllum. Ionizing radiation has a similar effect.

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Using this book

This book has been designed so that it can be readily consulted by clinicians on the use of therapeutic drugs in pregnancy. It gives information on possible teratogenic effects of all drugs in current use. For each drug the pharmacological actions are briefly described, as well as the effects on human pregnancy and lactation. A summary of animal pharmacology during pregnancy is included.

We wish to emphasize:

- (1) that the information given in this book is not to be regarded as absolute;
- (2) that data from experimental animals cannot be directly applied to man.

The drugs are listed according to pharmacological type and therapeutic use, grouping together drugs with similar clinical indications. In addition to the general names of the drugs (which are indexed) we have included chemical formulae and molecular weights, so as to precisely characterize them. Some proprietary names are included.

Each chapter (for example, 'General anaesthetics') includes a list of the drugs discussed in that chapter, with a codification of the recommendations for the use or non-use of each drug. The codes used are:

- NC: Drugs not contra-indicated either in pregnancy or labour, when used in the normal therapeutic doses.
- P: Precaution – drugs to be used with care, and only when absolutely necessary.
- C: Drugs that are contra-indicated. Their use should be limited to cases of exceptional difficulty, and when recourse to other less contra-indicated drugs is not possible. In some instances, the drugs are absolutely contra-indicated in only certain stages of pregnancy (trimesters 1,2,3), in labour, or during lactation.

The entry relating to a particular drug starts with a single-sentence summary of recommendations. Where there is contra-indication, or the need for precaution, there follows a table showing the appropriate codes (C or P) and the stages to which they apply. Blanks in the table, or indeed the absence of a table, imply that the drug is not contra-indicated. Further detail is given in the text.

For some drugs we have found no information on clinical experience or animal experiments. The entries for these drugs are collected together at the

ends of the relevant chapters or sections of chapters: they are collectively preceded by a row of asterisks * * * * *

Comparative table of embryonic development in diverse animal species.

Compilation of data existing in current literature.

Gestational age is expressed in days (weeks).

	Man	Rat	Mouse	Rabbit	Chicken
Duration of pregnancy	280 (40)	22 (3.1)	19 (2.7)	33 (4.7)	21 (3) (incubation)
Implantation of blastocyst	7 (1)	5-6 (0.7-0.9)	7 (1)	6 (0.9)	—
Initiation of cardiac action	22 (3.1)	10 (1.4)	—	—	1.5 (0.2)
Pronephros					
Mesonephros	25 (3.6)	12 (1.7)	9.5 (1.4)	—	1.75 (0.25)
Thyroid outline	27 (3.9)	10 (1.4)	8.5 (1.2)	—	1.8 (0.25)
Outline of upper limbs	27 (3.9)	10.5 (1.5)	9.3 (1.3)	10.5 (1.5)	2.2 (0.3)
Outline of metanephros					
Outline of lungs	28 (4)	12.2 (1.75)	9.6 (1.4)	—	3 (0.4)
Outline of lower limbs	30 (4.3)	—	10.3 (1.5)	11 (1.6)	2.5 (0.4)
Initiation of ossification	41 (5.9)	17.5 (2.5)	12.5 (1.8)	—	8 (1.1)
Outline of ducts of Müller	40 (5.7)	13.5 (1.9)	—		4 (0.6)
Outline of testicles	45 (6.4)	14.5 (2.1)	—	20 (2.9)	5.5 (0.8)
Closure of palate	57 (8.1)	16.5 (2.4)	15 (2.1)	19.5 (2.8)	—

Part 3

Diuretics

1. DIURETICS

The diuretics are drugs which increase urine flow and modify the excretion of solutes. They are classified on the basis of their chemical structure and their mechanism of action.

THIAZIDE DIURETICS – these inhibit sodium and chloride reabsorption in the convoluted proximal tubule and increase excretion of potassium in the distal tubule. They also have an antihypertensive effect and reduce glomerular filtration.

MERCURIAL DIURETICS – these depress active reabsorption of sodium, and are dependent for their intensity of action on urinary pH.

INHIBITORS OF CARBONIC ANHYDRASE – these diminish bicarbonate reabsorption and reduce intra-ocular pressure.

INHIBITORS OF ALDOSTERONE.

OSMOTIC DIURETICS – these readily pass through the glomerulus and are not reabsorbed in the tubules.

MISCELLANEOUS DIURETICS

During pregnancy diuretic therapy is used both in the presence and absence of E.P.H. gestosis. The following diuretics are discussed:

	Recommendation	Page
<i>Thiazide diuretics</i>		
Chlorothiazide	P	2
Hydrochlorothiazide	P	4
	(C during lactation)	
Hydroflumethiazide	P	5
Polythiazide	P	6
	(C during lactation)	
Bendroflumethiazide	P	7
Trichlormethiazide	P	8

Quinethazone	P	9
Fenquizone	P	10
<i>Mercurial diuretics</i>		
Meralluride	C	11
<i>Inhibitors of carbonic anhydrase</i>		
Acetazolamide	P	11
Dichlorphenamide	P	13
Ethoxyzolamide	P	14
<i>Inhibitors of aldosterone</i>		
Spironolactone	NC	15
<i>Osmotic diuretics</i>		
Mannitol	NC	16
<i>Miscellaneous diuretics</i>		
Clopamide	NC	17
Clorthalidone	NC	18
	(P during lactation)	
Frusemide	NC	19
Mefruside	NC	19
Triamterene	NC	20
Ethacrynic acid	NC	21

The thiazide diuretics should be used with care in the last trimester, in labour, and in the puerperium, because of possible disturbances of electrolyte balance, myelotoxicity in the neonate, and an inhibitory effect on lactation.

The mercurial diuretics are in fact little used, and are contra-indicated because of their toxicity.

The carbonic anhydrase inhibitors must be used with care in the last trimester because they can alter acid-base and electrolyte balance in the foetus and the neonate. Some experimental data, which have been confirmed in man, suggest a possible teratogenic action when carbonic anhydrase inhibitors are administered during embryogenesis.

Aldosterone inhibitors, osmotic diuretics, and the miscellaneous group which have various chemical structures, are not contra-indicated in pregnancy at normal therapeutic doses.

1.1 Thiazide diuretics

Chlorothiazide

Saluric, 6-chloro-7-sulphamyl-1, 2, 4-benzothiodiazine-1, 1-dioxide
(MW 295.74)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Chlorothiazide is the principal benzothiazide derivative, and its mechanism of action is by means of inhibition of sodium and chloride reabsorption in the convoluted proximal tubule. Its efficacy is not diminished by variations in acid-base equilibrium, as occurs with acetazolamide or the mercurial diuretics. Chlorothiazide also has an antihypertensive effect, reduces elimination of uric acid, causes hyperglycaemia, and exacerbates diabetes. It is used in the treatment of oedema, nephrosis, diabetes insipidus, and in pregnancy.

Chlorothiazide crosses the placental barrier [1, 12, 13, 16] and passes into breast milk [5, 7]. No cases of teratogenicity have been observed [3, 4] which could be linked to the use of the drug in pregnancy. It has, however, been claimed that chlorothiazide can cause thrombocytopenia in the neonate, as do other thiazides, if taken in the last trimester [2, 11, 14, 17]. Following prolonged use, metabolic disturbances may appear (hyponatraemia, hypokalaemia, hyperglycaemia) in pregnant women [5, 6, 7, 15, 16]. The foetus appears to be relatively resistant to variations in maternal electrolytes, even although the occasional case of foetal hyponatraemia has been reported [6].

In the rat, subcutaneous doses of 250 mg/kg from the 10th to the 11th day of pregnancy, and doses of 166 mg/kg from the 8th day to the end of pregnancy, were not teratogenic [9, 10].

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Hydrochlorothiazide

Esidrex, Esidrex-K,

6-chloro-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide

(MW 297.72)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		C

To be used with care in pregnancy and during lactation.

A diuretic of the benzothiazide series, hydrochlorothiazide produces an increase in sodium, potassium, and chloride excretion, and consequently causes diuresis. The natriuretic effect develops as a result of inhibition of sodium reabsorption in the proximal tubule, while the kaliuretic effect is probably due to an increase in excretion of potassium in the distal tubule. Like other thiazide diuretics, hydrochlorothiazide also has an antihypertensive effect, reduces glomerular filtration, and increases glycaemia.

Hydrochlorothiazide crosses the placental barrier [1, 21]. No cases of teratogenicity linked to the use of the drug in pregnancy have been reported. The possibility of thrombocytopenia, aplasia of the bone marrow, and death of the neonate, caused by the use of hydrochlorothiazide in the last trimester, has been reported [2, 3, 4, 5, 6, 12, 18, 19, 20, 22]. Its prolonged use may cause serious electrolyte disturbances, with effects on the foetus [2, 13, 14, 15, 16, 21].

No complications occurred during labour in women who had taken the drug in pregnancy [7, 11, 17]. Hydrochlorothiazide passes into breast milk, and therefore should not be taken during lactation [1].

In the mouse, rat, and rabbit, hydrochlorothiazide was neither embryo-foetotoxic nor teratogenic [8, 9]. In the rat, oral doses of 10 mg/kg from the 1st to the 20th day of pregnancy and subcutaneous doses of 250 mg/day from the 9th to the 12th day of pregnancy did not affect foetal development [8, 9]. In the rabbit, similar oral doses from the 7th to the 15th day of pregnancy were not embryofoetotoxic [8].

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Hydroflumethiazide

Hydrenox, Rautrax, Aldactide,

6-trifluoromethyl-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide
(MW 331.29)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Hydroflumethiazide has diuretic and antihypertensive actions. It inhibits tubular reabsorption of sodium and chloride with minimal loss of potassium and bicarbonate. It causes a gradual reduction in systolic and diastolic blood pressure. Hydroflumethiazide is used in the therapy of oedema, hypertension, nephrosis, and in pregnancy.

Hydroflumethiazide crosses the placental barrier [12]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2]. Some authors advise care in the use of hydroflumethiazide in pregnancy because its safety has not been sufficiently well documented, particularly with regard to the foetus [3, 4]. It has been claimed that as a result of foetal hyponatraemia, prolonged use of thiazide diuretics in the first trimester could cause puerperal thrombocytopenia in the neonate, and medullary aplasia and neonatal death [7, 8, 9, 10, 11, 12, 13].

No experimental studies have been reported on the use of hydroflumethiazide in pregnancy in laboratory animals.

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Polythiazide

Nephрил, 2-methyl-3, 4-dihydro-3-(2, 2, 2-trifluoroethyl-thiomethyl)-6-chloro-7-sulphamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide (MW 439.9)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		C

To be used with care in pregnancy, and is contra-indicated during lactation.

Like other thiazides, polythiazide increases renal excretion of sodium and chloride. It also slightly increases elimination of potassium. It inhibits carbonic anhydrase, reduces glomerular filtration, and diminishes the excretion of uric acid and calcium. Polythiazide has an antihypertensive action, and is used to treat oedema, nephrosis, and hypertension.

Polythiazide crosses the placental barrier [8]. It is used in the therapy of oedema in pregnancy, and there are no side effects in the mother or the foetus [1]. Administered to 51 women with oedema in the third month of pregnancy, at a dose of 1–2 mg/day for a period of 2–12 weeks, polythiazide was without side effects, and it did not cause foetal dehydration, even when therapy was continued throughout the pregnancy [1].

It should be noted that after treatment with thiazide diuretics in pregnancy, cases of thrombocytopenia puerpera, medullary aplasia, and neonatal death have been reported [3, 4, 5, 7, 9].

Polythiazide administered during the first 8 days after birth inhibits lactation [2].

No experimental studies have been found on the use of polythiazide in pregnancy in laboratory animals.

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Bendroflumethiazide

Abicol, Aprinox, Centyl-K, Neo-Naclex,
3-benzyl-3,4-dihydro-6-(trifluoromethyl)-2*H*-1,2,3-benzothiadiazine-7-sulphonamide-1,1-dioxide (MW 421.41)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Bendroflumethiazide produces a marked increase in urinary excretion of water, sodium, chloride, and also, to a lesser extent, bicarbonate and potassium. Even although the loss of potassium is minimal, concomitant administration of the latter is essential during prolonged treatment, in order to avoid disturbances in acid-base equilibrium. Bendroflumethiazide also has an antihypertensive action, and slightly reduces glomerular filtration and excretion of uric acid and calcium. It is used to treat oedema and hypertension.

Bendroflumethiazide rapidly crosses the placental barrier and is found in breast milk [1, 2]. In obstetrics, bendroflumethiazide is used in the therapy of oedema and hypertension. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2, 3, 4, 5, 6, 13, 14, 15, 16, 17, 19, 20, 21, 22]. Bendroflumethiazide administered to 18 pregnant women at a dose of 5 mg/day for 3 weeks caused an improvement in oedema and loss of weight [19]. In 50 pregnant women the drug was administered at a dose of 2.5–10 mg/day with satisfactory effects on oedema [20]. Twenty-eight patients in the third trimester were treated with bendroflumethiazide at a dose of 5 mg/day for 1 week, after which time oedema and albuminuria had disappeared [21]. Twenty pregnant women were treated with the drug at a dose of 2.5–10 mg/day for 1–4 weeks. A satisfactory weight loss was obtained [17]. Twenty-two pregnant women were treated with 10 mg/day for several months. No side effects were noted in the mother or the foetus [18]. At doses of 10 mg/day for a period of 4–40 days in patients with toxæmia, bendroflumethiazide did not cause foetal death or neonatal thrombocytopenia [6].

It should, however, be noted that the thiazide diuretics can in some cases induce medullary aplasia in the foetus, leading to a reduction in megakaryocytes with the possible appearance of thrombocytopoenic purpura, which can be fatal [1,7,8,9,10,24,25].

Bendroflumethiazide passes into breast milk in small amounts [23].

In the rat, bendroflumethiazide was neither embryofoetotoxic nor teratogenic [12].

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Trichlormethiazide

Flutra, Metahydrin,

6-chloro-7-sulphamyl-3-dichloromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (MW 380.67)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Trichlormethiazide is more effective than other oral diuretics of the thiazide group at the same dosage. It does not seriously disturb electrolyte equilibrium

and may be administered for long periods. It acts synergistically with derivatives of digitalis and with other hypotensive drugs.

Trichlormethiazide is used in the treatment of oedema in pregnancy without causing side effects in the mother or the foetus [1, 2, 11, 12, 13, 14, 15, 16, 17]. Administered at a dose of 8 mg/day in 35 patients from the 5th to the 8th month of pregnancy for a period of about 1 week, the drug did not have harmful effects [1]. A dose of 4–8 mg/day in 46 pregnant women for periods of 2 weeks to several months was without side effects in the mother and the foetus [2].

Thiazide diuretics may provoke thrombocytopenia in the neonate, as a result of depression of megakaryocytes and of medullary aplasia, and may even cause foetal death [3, 4, 5, 6, 7, 8, 9, 10, 18].

No experimental studies have been found on the use of trichlormethiazide in pregnancy in laboratory animals.

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Quinethazone

Aquamox,

7-chloro-2-ethyl-1, 2, 3, 4-tetrahydro-6-sulphamylquinazoline-4-one
(MW 289.76)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Quinathazone is a benzothiadiazine diuretic which does not act on carbonic

anhydrase, but on renal tubular transport of sodium and chloride. It also has a hypotensive effect. Compared to chlorothiazide, quinathazone is more potent because it also acts distally, and probably on the ascending tract of the loop of Henle. It may cause slight hyponatraemia.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. Certain authors [1, 2], however, advise care in the use of quinathazone in pregnancy, because of disturbances in water and electrolyte balance which may occur in the foetus following prolonged administration. Other reservations regarding methiazides should also be noted (see hydrochlorothiazide, page 4).

No experimental studies have been described on the use of quinathazone in pregnancy in laboratory animals.

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Fenquizone

2-phenyl-6-sulphonamido-7-chloro-1, 2, 3, 4-tetrahydro-4-quinazolinone

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Fenquizone is a saluretic with a quinazolinone structure which acts by blocking reabsorption of sodium in the proximal tubule and the ascending branch of the loop of Henle, as well as in the proximal section of the convoluted distal tubule. Fenquizone causes an increase in diuresis with elimination of chloride and sodium but not potassium. In addition, it also has a hypotensive action. Fenquizone is rapidly absorbed from the digestive tract, is not metabolized, and forms stable bonds with plasma proteins.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, the same precautions apply as with other thiazides (see hydrochlorothiazide, page 4).

In the rat and rabbit, fenquizone at doses 10–30 times therapeutic was neither embryofetotoxic nor teratogenic [1].

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1.2 Mercurial diuretics

Meralluride

N-((2-methoxy-3-((1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurin-7-yl)mercuri)propyl)-carbamoyl)succinamic acid (MW 448.86)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic		C	C		

Contra-indicated in pregnancy.

Meralluride is a diuretic which acts principally on the proximal convoluted tubule, where it inhibits active reabsorption of sodium and blocks potassium secretion. The diuretic response is dependent upon blood chloride concentration, pH, and sodium chloride intake in the diet. Meralluride is an organic substance related to mercury and complexed with theophylline to facilitate its absorption. The mercurial diuretics are used mainly in oedema resulting from cardiac decompensation, and are contra-indicated in renal insufficiency. Mercurial compounds, even in low concentrations, inactivate sulphhydryl enzymes and interfere with cellular metabolism.

The use of mercurial diuretics in pregnancy is not advised, because of their direct toxic action on the kidneys, which can cause vascular–renal syndromes or aggravate pre-existing renal insufficiency [1, 2].

In the rat, administration of mercurial diuretics in pregnancy has produced embryotoxic effects [3].

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1.3 Inhibitors of carbonic anhydrase

Acetazolamide

Diamox, 2-acetyl-amino-1,3,4-thiadiazole-5-sulphonamide (MW 222.25)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				P	
Chronic	P		P		

To be used with care in pregnancy.

Acetazolamide is a heterocyclic sulphonamide, and a potent inhibitor of carbonic anhydrase in the renal tubules, with consequent diminution of bicarbonate reabsorption. Acetazolamide facilitates excretion of bicarbonate rather than of chloride ions. Acetazolamide causes alkalization of the urine and moderate metabolic acidosis. It is used as a diuretic, and also as an anti-epileptic and in the symptomatic treatment of glaucoma. Acetazolamide inhibits the role of carbonic anhydrase in calcification in some species of animals (echinoderms, molluscs) [1].

Acetazolamide crosses the placental barrier [2, 8, 21]. It has been used in the therapy of gestosis, at doses of 250 mg every 3 days and up to 1 g/day without side effects in the foetus [4]. In a retrospective study on 404 malformed infants (in a total of 21526 births) 40 were from mothers treated with acetazolamide in pregnancy [20]. However, the authors [20] maintain that this frequency of malformations does not differ from the spontaneous rate, and thus cannot be attributed to teratogenic effects of acetazolamide.

In labour, on the other hand, administration of acetazolamide can provoke metabolic foetal acidosis, since the foetal kidneys can also respond to carbonic anhydrase during the last part of intra-uterine life [2]. The disturbance of salt and water equilibrium which can result from prolonged use of acetazolamide may cause [3] or aggravate [2] eventual polyhydramnios. Administered intravenously to pregnant women from 30 to 90 minutes before birth, it can cause an increase in diuresis and elimination of sodium and potassium in the first 24 hours of life [2]. The appearance of acidosis, hypokalaemia, and hyponatraemia in the foetus has been noted by other authors [6, 7, 21].

Although no embryofoetotoxic or teratogenic effects have been reported which could be attributed with certainty to the use of acetazolamide, we advise against its use during the first trimester, on the basis of experimental data at present available. Other workers support this view [9]. The possibility of agranulocytosis, leucopenia, aplastic anaemia, and jaundice has been described [3].

In laboratory animals, acetazolamide was embryofoetotoxic and teratogenic [1, 10, 11, 12, 13, 14, 15, 16, 17]. In order to explain the teratogenic effects of the drug, some authors [18] have induced a respiratory and metabolic acidosis in the rat, but no malformations were produced. Administration of potassium during treatment with acetazolamide has reduced the incidence of malformations [18]. In the rat, at doses of 0.3–0.6% in the diet from the 7th to the 10th day of pregnancy, acetazolamide caused hydrocephalus, phocomelia, oligodactyly, hydronephrosis, and malformations of the cardiovascular system and the eye [10, 11]. Subcutaneous doses of 500–1000 mg/kg from the 10th to the 11th day of pregnancy caused hydrocephalus, phocomelia, oligodactyly, hydronephrosis, and malformations of the cardiovascular system [11, 12]. Oral doses of 80–640 mg/kg from the 9th to the 11th day of pregnancy were foetotoxic, causing inhibition of foetal growth, and teratogenic [13]. Injected into the

embryonic sac at doses of 0.1–0.5 mg/kg on the 11th day of pregnancy, acetazolamide was teratogenic [14].

In the mouse, a dose of 0.1% in the diet, throughout pregnancy, was teratogenic [10]. Given subcutaneously at doses of 300–1000 mg/kg from the 9th to the 11th day of pregnancy, acetazolamide was embryofoetotoxic and teratogenic [15].

In the hamster, a dose of 300–1200 mg/kg given subcutaneously on the 9th day of pregnancy was teratogenic (phocomelia, oligodactyly) [16].

In the monkey, an oral dose of 600–1200 mg/kg given as a single administration or repeated from the 22nd to the 27th day of pregnancy was embryofoetotoxic [17].

In chick embryo, acetazolamide selectively inhibited morphogenesis or otolytes if injected into the albumin of the egg on the 4th day of incubation, before morphogenesis of otolytes had begun and activation of calcium metabolism in the labyrinthine membrane had been affected [1].

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Dichlorphenamide

Oratrol, Daranide, 1, 3-disulphonamido-4, 5-dichlorobenzene (MW 305.16)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				P	
Chronic			P		

To be used with care in pregnancy.

Dichlorphenamide is an inhibitor of carbonic anhydrase with pharmacological actions similar to, but not identical with, those of acetazolamide. After oral administration, it causes an increase in the excretion of bicarbonate, sodium, and potassium, but in contrast to other carbonic anhydrase inhibitors, it also increases the excretion of chloride, thus inducing a slight metabolic acidosis and anti-epileptic effect. Its therapeutic use is limited exclusively to treatment of glaucoma.

Dichlorphenamide should be used with care in pregnancy, because, like all carbonic anhydrase inhibitors, it is potentially toxic to the foetus, producing metabolic acidosis [1, 2].

In laboratory animals, dichlorphenamide was teratogenic [3, 4, 5, 8]. In the rat, a dose of 0.6% in the diet throughout pregnancy was teratogenic [3]. In the mouse, subcutaneous doses of 2.4–3.6 mg/day in a single administration or divided doses, from the 13th to the 18th day of pregnancy, were teratogenic, causing malformations of the ear [4]. In chick embryo, injection of dichlorphenamide on the 4th day of incubation at a dose of 2 mg per egg caused elective inhibition of morphogenesis of otoliths [8]. Administration of ADP reduces the teratogenic effects of dichlorphenamide [5].

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Ethoxzolamide

Cardrase, Ethamide,

6-ethoxy-2-benzothiazolesulphonamide (MW 258.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				P	
Chronic			P		

To be used with care in pregnancy.

Ethoxzolamide is an inhibitor of carbonic anhydrase which produces diuresis by diminution of bicarbonate reabsorption. The increased elimination of

bicarbonate in the urine is counterbalanced by a parallel loss of cations, mainly sodium but also potassium, and is accompanied by a reduced loss of chloride ions. The urine tends to become alkaline.

All carbonic anhydrase inhibitors are potentially damaging to the foetus, causing metabolic acidosis, and therefore ethoxzolamide should be used with care in pregnancy [1, 2].

In laboratory animals, ethoxzolamide was embryofetotoxic and teratogenic [3, 5]. In the rat, doses of 0.3–0.6% in the diet throughout pregnancy were embryofetotoxic and teratogenic (hydrocephalus, malformations of the cardiovascular system and the eye, phocomelia, oligodactyly, and hydro-nephrosis) [3]. In chick embryo, injection of 2–4 mg/egg into the albumin on the 4th day of incubation produced inhibition of morphogenesis of otolytes [5].

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1.4 Inhibitors of aldosterone

Spironolactone

Spiroctan, Diatensec, Aldactone, γ -lactone of

17-hydroxy-7-mercapto-7-oxo-17- α -pregn-4-ene-21-carboxylic acid 7-acetate (MW 416.6)

Not contra-indicated in pregnancy.

Spironolactone is a steroid diuretic with a competitive action on renal receptors for aldosterone and DOCA. In the distal convoluted tubule, spironolactone causes an increase in secretion of sodium and chloride, and a diminution in elimination of potassium, hydrogen ions, and ammonia. After administration of spironolactone, no effects of a hormonal nature were noted, except for isolated observations of gynaecomastia and amenorrhoea. Spironolactone can produce hyperkalaemia, hyperazotaemia, and slight acidosis. It potentiates the action of hypotensives.

Some authors have advised against the use of spironolactone in the first trimester, but have given no reasons [1, 2, 9, 15]. In obstetrics, the drug is used in the treatment of gestosis, since alterations in the aldosterone response have often been observed in this condition. In such cases, variations in diuresis, elimination of sodium and arterial pressure are not constant. In gestosis therapy, spironolactone tends to normalize serum lipoproteins [3]. No toxic effects have been observed in the mother [3, 4, 5, 6, 10, 11, 12, 13], or in the neonate, as evaluated by Apgar score [4, 14].

In the mouse, rat, and rabbit, spironolactone was neither embryofetotoxic nor teratogenic [7, 8]. In the mouse, oral doses of 2 mg/kg and 20 mg/kg from the 6th to the 15th day of pregnancy were not teratogenic [7]. In the rat, oral doses of 10 mg/kg from the 1st to the 20th day of pregnancy did not affect foetal development [8]. In the rabbit, oral doses of 10 mg/kg from the 7th to the 15th day of pregnancy did not affect foetal development [8].

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1.5 Osmotic diuretics

Mannitol

(MW 182.17)

Not contra-indicated in pregnancy.

Mannitol is rapidly filtered by the glomerulus and is not reabsorbed, thus producing an osmotic diuresis. The osmotic diuretics have the unique characteristic of being active in conditions such as hypovolaemic shock and serious dehydration, when renal haemodynamics are compromised and glomerular filtration reduced. Since reabsorption of mannitol is virtually impossible, this substance is quantitatively excreted in the urine, and it thus assures a sufficient urine volume, provided that there are no serious lesions in the tubular epithelium. High doses of mannitol also increase urinary excretion of electrolytes (sodium, potassium, chloride). Mannitol is absorbed only very slightly when administered orally, and is therefore given intravenously. It is used to treat acute renal insufficiency, and the oliguria which follows is of value in reducing intra-ocular and cerebral spinal fluid pressure, as well as intracranial pressure, by increasing the osmolarity of the plasma.

Mannitol crosses the placental barrier [8]. The drug has been used in pregnancy with no side effects in the mother or the foetus [1]. Our clinical

experience is similar [5,6,7]. Administration of very high doses may rapidly reduce the volume of the amniotic fluid, and so dehydrate the foetus [9].

In the rat, intravenous administration of a solution of 25% mannitol at a dose of 5 ml/100 g body weight on the 16th day of pregnancy caused haemorrhage of the foetal extremities. This was attributed to a reduction in volume of the amniotic fluid, and consequently of the uterus and placenta, which in turn led to an increase in foetal blood pressure because the blood in the placenta was 'pushed' towards the foetus, or because the counter-pressure of the amniotic fluid had been reduced [2,3]. This hypothesis has not been verified experimentally.

In the rabbit, mannitol administered intravenously towards the end of pregnancy caused foetal dehydration but not haemorrhage [4].

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1.6 Miscellaneous diuretics

Clopamide

Brinaldix, Brinaldix-K, Viskaldix,
N-(*cis*-2',6'-dimethyl-(1')-piperidyl)-amide of 3-sulphamyl-4-chloro-benzoic acid (MW 345.86)

Not contra-indicated in pregnancy.

Clopamide is a sulphonamide diuretic with a pharmacological action similar to that of the thiazides.

Clopamide has been employed successfully in association with reserpine and dihydroergocristine in the treatment of gestosis and pre-eclampsia, with no side effects in the mother or the foetus [1,2,3,4].

No experimental studies have been found on the use of clopamide in pregnancy in laboratory animals.

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Chlorthalidone

Hygroton, Opnesoretic, Tenoret, Tenoretisco,

1-oxo-3-(3'-sulphamyl-4'-chlorophenyl)-3-hydroxy-isoindoline (MW 338.78)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic					P

Not contra-indicated in pregnancy, but should be used with care during lactation.

Chlorthalidone is a sulphonamide diuretic, a derivative of isoindoline, which inhibits tubular reabsorption of sodium and chloride. It is also antihypertensive, because it causes increased excretion of sodium and, to a lesser extent, potassium.

Chlorthalidone crosses the placental barrier [1]. It has been used successfully in the treatment of excessive weight, oedema, and gestosis in the third trimester, with no side effects in the mother [1, 2, 3, 4, 5, 6, 10, 12, 13, 14, 15], or the foetus [6, 7, 14, 15, 16]. Our own clinical experience supports this view. Cases of excessive hypokalaemia have been noted, together with metabolic alkalosis followed by the death of the foetus or premature birth [8], and neonatal dehydration and electrolyte imbalance have also been observed [1].

Chlorthalidone passes into breast milk in sufficient quantities to cause diuresis in the infant [17].

In the rabbit, rat, mouse, and hamster, chlorthalidone at doses of 50–2000 mg/kg was not teratogenic [9].

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Frusemide

Lasix, 4-chloro-*N*-(2-furylmethyl)-5-sulphamyl-anthranilic acid (MW 330.77)

Not contra-indicated in pregnancy.

Frusemide is a derivative of anthranilic acid, and is structurally similar to the thiazides, but its pharmacological actions are markedly different. Unlike the thiazides, frusemide increases elimination of sodium and chloride without affecting potassium exchange. Its mechanism of action is based on the inhibition of sodium, chloride, and water reabsorption in the proximal tubules, in the ascending part of the loop of Henle and in the distal tubule. This action is independent of pH variations. Frusemide increases urinary excretion of serotonin and calcium. It also tends to produce alkalosis by elimination of chlorides rather than of bicarbonates, and by depletion of potassium. Frusemide is used in the therapy of oedemas of cardio-hepatic and renal origin, of acute pulmonary oedema and of renal insufficiency.

Frusemide crosses the placental barrier [5, 9]. It has been used in pregnancy, in labour, and in the puerperium in cases of excessive weight gain, oedema, hypertension, and gestosis, with satisfactory results [1, 2], and with no embryo-foetotoxic or teratogenic effects [3, 4, 6, 7, 8, 9]. Our own clinical experience supports this view. Neonatal electrolyte disturbance may occur. Intravenous administration of 40–750 mg to 14 pre-eclamptic patients in the 32nd to 42nd week of pregnancy caused a significant increase in the concentration of creatinine in the amniotic fluid. This was independent of maternal creatinine concentrations [10].

No experimental studies have been found on the use of frusemide in pregnancy in laboratory animals.

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Mefruside

Baycaron,

N-(4'-chloro-3-sulphamoylbenzenesulphonyl)-*N*-methyl-2-aminomethyl-2-methyl-tetrahydrofuran (MW 382.9)

Not contra-indicated in pregnancy.

Mefruside is a saluretic which differs chemically from other diuretics,

and which has an intense antihypertensive action, which is linked to increased sodium excretion accompanied by minimal elimination of potassium. It affects mainly the ascending loop of Henle. Mefruside is used in the treatment of oedema and hypertension.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 6]. In 56 patients with gestosis in the third trimester, administration of mefruside at doses of 25–75 mg/day did not cause any congenital malformations or embryofoetotoxic effects [2]. However, some authors, and the manufacturers, advise caution in its use in pregnancy [3, 4, 5].

In the rat, mefruside in oral doses of 1 g/kg from the 6th to the 16th day of pregnancy was not embryofoetotoxic [5].

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Triamterene

Dytac, Dyazide, Dytide,

2,4,7-triamino-6-phenylpteridine (MW 253.3)

Not contra-indicated in pregnancy.

Triamterene is a derivative of pteridine, and is similar to folic acid, but does not compete *in vivo* for this substance. Its diuretic action is based upon the elimination of sodium chloride, without loss of potassium. In fact, it tends to inhibit the secretion of potassium in the distal tubule. Triamterene acts independently of pH, and is slightly toxic. It can produce hyperkalaemia. It is used to treat oedema, mainly in association with other diuretics.

Triamterene has been used in the therapy of gestosis arising from oedema, with no side effects in the mother or the foetus [1, 2, 3]. Our own clinical experience is similar. Others [6] advise care in its use during the first trimester.

In the rat, triamterene orally at doses of 11.1–32 mg/kg from the 8th to the 9th day of pregnancy or solutions of 1 mg/ml in water given orally from the 9th to the 13th day of pregnancy were neither embryofoetotoxic nor teratogenic [4, 5].

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Ethacrynic acid

Edecrin, (2,3-dichloro-4-(2-methylene-butyryl)phenoxy) acetic acid
(MW 303.15)

Not contra-indicated in pregnancy.

Ethacrynic acid is a derivative of an aryloxy-acetic acid which inhibits reabsorption of sodium and chlorides, mainly in the ascending loop of Henle. It is rapidly absorbed after oral administration and binds to plasma proteins, whence it is partially metabolized. Like the mercurial diuretics, ethacrynic acid combines with sulphhydryl groups, which are necessary for the action of certain enzymes and of insulin. Ethacrynic acid tends to produce metabolic alkalosis because it results in the elimination of chlorides and bicarbonates and also of hydrogen ions and potassium. It reduces the elimination of uric acid and increases loss of calcium. It is used in the treatment of oedema of various origins, where it does not compromise renal function.

Ethacrynic acid crosses the placental barrier [5]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3,4], but prolonged treatment can give rise to electrolyte disturbance in the foetus.

No experimental studies have been described on the use of ethacrynic acid in pregnancy in laboratory animals.

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Part 4

Drugs active on the digestive system

	Page
1. Antacids	24
2. Adsorbents and astringents	29
3. Anti-ulcer drugs	31
4. Cholagogues and choleretics	34
5. Hepatoprotectors	42
6. Laxatives and regulators of gastrointestinal motility	46

1. ANTACIDS

The antacids tend to raise gastric pH by acting as a buffer. Drugs with a parasympatholytic action give the same result by reducing secretion of hydrochloric acid, and are described in the section dealing with substances active on the autonomic nervous system. The antacids reduce activity of pepsin and absorption of certain drugs by changing pH. Their effectiveness is dependent upon solubility and on the time for which they remain in the stomach.

During pregnancy, some patients have increased gastric acidity, which arises from autonomic disturbance. Symptomatic treatment with antacids may be of use in this situation.

Drugs included in this section are compounds of aluminium and magnesium, which are less soluble, dissociate less, and are only slightly absorbed. None of them is contra-indicated in pregnancy, and the following are discussed in this chapter:

	Recommendation	Page
Aluminium hydroxide	NC	24
Alnasile	NC	25
Aluminium glycinate	NC	25
Aloglutamol	NC	26
Magaldrate	NC	26
Magnesium hydroxide	NC	26
Polyalexitol	NC	27

There is insufficient information available on the following drugs to recommend their use in pregnancy: bismuth aluminate, sodium citrate, poliamine (see page 27–28).

A retrospective study by Nelson and Forfar [1] has shown that among mothers of malformed infants, there was a significantly larger number who had taken antacids, iron preparations, and cough sedatives during pregnancy than in a control group. We do not place much reliance on this work, and therefore do not share the conclusions of the authors.

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Aluminium hydroxide

Algedrate, colloidal aluminium hydrate (MW 77.99)

Not contra-indicated in pregnancy.

Aluminium hydroxide hydrate has a long duration of action, possesses astringent activity, and may cause constipation. It should be remembered that because of its absorbent properties, aluminium hydroxide can fix small quantities of phosphates and vitamins in the intestine. Although this is not important, these factors should be made up in the diet.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

No experimental studies have been described on the use of aluminium hydroxide in pregnancy in laboratory animals.

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Alnasile

silicates of aluminium and sodium (MW 282.4)

Not contra-indicated in pregnancy.

Alnasile is a double silicate of aluminium and sodium which is not absorbed in the gastrointestinal tract.

Alnasile is used in the treatment of ulcers and of gastric pyrosis in pregnancy. It has no side effects in the mother or the foetus [1], and our clinical experience supports this view.

No experimental studies have been found on the use of alnasile in pregnancy in laboratory animals.

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Aluminium glycinate

Prodexin, basic aluminium aminoacetate (MW 135.1)

Not contra-indicated in pregnancy.

Like other analogous salts, aluminium glycinate is an antacid which is insoluble in water. It is administered in the form of tablets or a suspension, and acts as a buffer against hyperchlorhydria.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

No experimental studies have been described on the use of alnasile in pregnancy in laboratory animals.

Bibliography

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[3] *Dictionnaire Vidal* - O.V.P. Ed. - Paris, 1975.
[4] Massam D.: *A.B.P.I. Data Sheet Compendium* - Butler & Tanner Ed. - London, 1975.

Aloglutamol

6-dihydroxyaluminium gluconate of tris-hydroxymethylaminomethane
(MW 377.0)

Not contra-indicated in pregnancy.

Aloglutamol has a buffering action, is not absorbed, and maintains the gastric pH between 3 and 5.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat and rabbit, aloglutamol was neither embryofoetotoxic nor teratogenic [12]. In the rat, oral doses of 100–200–400 mg/kg/day from the 6th to the 18th day of pregnancy were without harmful effects on the foetus or the mother [1]. In the rabbit, similar doses at similar times were likewise without harmful side effects [1].

Bibliography

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Magaldrate

magnesium hydrate aluminate (MW 425.3)

Not contra-indicated in pregnancy.

Magaldrate is an aluminate of magnesium, and has antacid properties.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of magaldrate in pregnancy in laboratory animals.

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Magnesium hydroxide

Maalox, Milk of Magnesia (MW 58.31)

(MW 58.31)

Not contra-indicated in pregnancy.

Magnesium hydroxide reacts with hydrochloric acid to form magnesium chloride. Its antacid action is slower than that of sodium bicarbonate, but more

prolonged. In the presence of an excess of magnesium oxide, the pH of gastric contents becomes slightly alkaline as a result of the formation of a small amount of magnesium hydroxide. In contrast to sodium bicarbonate, this does not produce systemic alkalosis, because there is no loss of chloride.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2], and the manufacturers have confirmed this [3].

No experimental studies have been described on the use of magnesium hydroxide in pregnancy in laboratory animals.

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- [3] Comunicazione personale della Ditta Granelli - Milano.

Polyalexitol

Actal, hexitol complex with aluminium polyhydroxide sodium monocarbonate

Not contra-indicated in pregnancy.

Polyalexitol is a complex of aluminium hydroxide and sorbitol. It is known that the buffer action of aluminium hydroxide is increased in the presence of this glycide. Polyalexitol is used as an antacid. The possibility of its use in the treatment of muscular cramp in pregnancy has been investigated, because it maintains a constant ratio between diffusible calcium and phosphate in the blood [1].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of polyalexitol in pregnancy in laboratory animals.

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Bismuth aluminate

aluminate of bismuth decahydrate (MW 915.9)

This drug is one of the most potent antacids in the bismuth group.

Sodium citrate

trisodium citrate (MW 294.12)

Sodium citrate is an intermediate compound in oxidative metabolism. Its pharmacological properties depend on its capacity to fix calcium ions (anti-coagulant action) and on its buffer action (alkalinizing activity in secondary metabolic acidosis and chronic renal insufficiency).

Polyamine

polyamine resin

Polyamine, incorrectly classified among the ion exchange resins, is made up of a lattice containing secondary and tertiary amine groups which can neutralize gastric acidity. This reaction is reversible in the intestine, by varying pH.

We have been unable to find any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. We therefore advise against their use in pregnancy and in women of childbearing age who are likely to conceive.

2. ADSORBENTS AND ASTRINGENTS

The adsorbents are substances which can bind bases, toxins, bacteria, and poisons. Some of the drugs described here have a protective action on the mucosa, thus preventing its contact with irritant agents, while others, such as simethicone, have water-repellent properties and are antifoaming agents. Others again, such as tannic acid, have an astringent action. None of these drugs is contra-indicated in pregnancy, and the following are described in this chapter:

	Recommendation	Page
Simethicone	NC	29
Zolimidine	NC	29

We maintain that there is insufficient information available on the use of the following drugs in pregnancy to recommend their use: kaolin, activated carbon, albumin tannate (page 30).

Simethicone or dimethicone

Asilone, Ovol, Rikospray silicone, Sylopal,
mixture of dimethylpolysiloxane and silica gel

Not contra-indicated in pregnancy.

Simethicone is a methylated derivative of silicone. It has a tensio-active and protective action on the skin and mucosa. It is used in the therapy of aerophagia and of meteorism.

Simethicone is not absorbed by the gastrointestinal mucosa, and is thus not contra-indicated in pregnancy [1, 2].

No experimental reports have been found on the use of simethicone in pregnancy in laboratory animals.

Bibliography

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- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.

Zolimidine

2-(*p*-methylsulphonylphenyl)-imidazo-(1,2-*a*)pyridine (MW 272.29)

Not contra-indicated in pregnancy.

Zolimidine is a synthetic substance, with a marked protective action on the gastro-duodenal wall.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In laboratory animals, studies have shown that zolimidine had no adverse effects on the course of pregnancy or the development of the foetus [1].

Bibliography

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* * * * *

Kaolin

aluminium silicate hydrate

Kaolin is a naturally occurring aluminium silicate hydrate with adsorbent action, and is used symptomatically in diarrhoea and in some types of poisoning.

Activated carbon

from poplar wood

Activated carbon is of vegetable origin, and has powerful adsorbent properties which are useful in the systematic treatment of meteorism, flatulence, and in the emergency treatment of certain types of poisoning.

Albumin tannate

combination of albumin with tannic acid

Tannic acid consists mainly of pentadigalloylglucose, and can precipitate proteins. Protein tannates, like albumin tannate, can be redissolved in alkaline solution. Tannic acid has an astringent action on the mucosa of the gastrointestinal tract, and thus causes constipation. Insoluble preparations of tannic acid are used in the therapy of diarrhoea, particularly in babies. Tannic acid is not absorbed as such in the gastrointestinal tract, but is absorbed in the form of gallic acid. It is hepatotoxic, if absorbed in sufficient quantities.

We have been unable to find information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. We therefore advise against their use in pregnancy and in women of childbearing age who are likely to conceive.

3. ANTI-ULCER DRUGS

In the treatment of peptic ulcer, the substances used in addition to the antacids and the parasympatholytics include those which promote healing of the mucosa or biosynthesis of mucin, as well as those which are anti-inflammatory or have a proteolytic action on gastric enzymes. None of these drugs is contra-indicated in pregnancy, and the following are discussed in this chapter:

	Recommendation	Page
Sulglycotide	NC	31
Gefarnate	NC	31
Carbenoxolone	NC	32

We do not believe that there is sufficient information available on the following drugs to recommend their use in pregnancy: methiosulphonium chloride, urogastone, clocanfamide, guaiazulene (page 32–33).

Sulglycotide

polysulphate ester of aglycopeptide

Not contra-indicated in pregnancy.

Sulglycotide is a glycopeptide which is isolated from the duodenal mucosa of the pig. It is characterized structurally as consisting of one part polysaccharide and one part peptide. The therapeutic effect of the drug on gastric and duodenal ulcers is dependent on the antipeptic action arising from the presence of a large number of free sulphonate groups on the molecule.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat and rabbit, sulglycotide was neither embryofoetotoxic nor teratogenic [1]. Administered to rats at a dose of 50–100–200 mg/kg by gastric intubation from the 1st to the 15th or the 1st to the 26th days of pregnancy, sulglycotide was without harmful effects [1].

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Gefarnate

Gefarnil, geranylfarnesylacetate (MW 400.62)

Not contra-indicated in pregnancy.

Gefamate heals and regenerates the gastro-duodenal mucosa, probably because of the presence of isoprene groups in the molecule. It is used in the treatment of gastric and duodenal ulcers.

Gefamate has been used to treat duodenal ulcer in pregnancy without harmful side effects [1].

In the rat and rabbit, oral doses of 20–200 mg/kg/day throughout pregnancy were neither embryofetotoxic nor teratogenic [2, 3].

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- [3] Penn G.H.: Pharmacology Department the Crookes Laboratories Lim. Report No. Ter. 12 - Comunicazione personale della Ditta De Angeli - Milano.

Carbenoxolone

Biogastrone, Bioral, Duogastrone,

3- β -hydroxy-11-oxo-(18- β)oleanen-(12)-oic-(30)ester
succinic-(3)-acid disodium salt (MW 570.74)

Not contra-indicated in pregnancy.

Carbenoxolone is a triterpenoid which is synthesized from the alkaloids present in liquorice (glycyrrhizinic acid). Carbenoxolone stimulates the synthesis of glycoproteins in the gastrointestinal epithelium, and thus leads to secretion of mucus and a slowing of cell turnover in the gastric wall. It is anti-inflammatory, diuretic, and tends to cause sodium retention, probably by potentiation of aldosterone. Carbenoxolone is used in the treatment of gastric ulcer.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers have confirmed this [1].

In the mouse, rat, and rabbit, administration of carbenoxolone at a dose of 125 mg/kg/day (four times therapeutic) did not have any effect on fertility, or the course of the pregnancy, and was neither embryofetotoxic nor teratogenic [2].

Bibliography

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Methiosulphonium chloride or vitamin U

methylmethionine sulphonium chloride (MW 199.6)

This drug is present in cabbage extract (*Brassica oleracea*) and stimulates the regeneration of the epithelium of the digestive tract (anti-ulcer action), and of

the skin. It also has a trophic effect on liver cells and on haemopoietic tissue (increases reticulocytes, neutrophils, platelets). Methiosulphonium chloride acts as a donor of methyl groups, as well as reintegrating sulphydryl groups necessary for oxidative phosphorylation and for the activity of many enzyme systems. The drug is also considered as 'radio-protective' in that it reduces oxidation of thiol substrates induced by radiation by means of the process of transulphuration. Its radio-protective action may also be attributed to the amino group, which inactivates free radicals produced by ionizing radiation.

Urogastrone

Clocamphamide

N-p-chlorobenzoyl-2-(2'-hydroxyethyl)aminomethyl-3-methylnorbornane (MW 321.8)

Guaizulene

1,4-dimethyl-7-isopropyl azulene (MW 198.3)

Guaizulene is a sesquiterpene, derived from azulene (cyclopentacycloheptene), with anti-inflammatory and antipyretic activity when applied locally. It is used to relieve irritation in the mucosa and the skin.

We have been unable to find any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. We therefore advise that they should not be used in pregnancy or in women of childbearing age who are likely to conceive.

4. CHOLERETICS AND CHOLAGOGUES

Choleretics are drugs which stimulate bile flow. Hydrocholeretics are thus called when they simply increase the volume of bile. True choleretics increase the quantities of solutes which are excreted. Cholagogues increase the mobility of the bile ducts. In this field, in addition to dehydrocholic acid and sorbitol, many drugs have been synthesized which combine a choleretic action with an antispastic one.

During pregnancy, the composition of bile changes, and there is a diminution in tone and in mobility of both intra- and extra-hepatic bile ducts, conditions which predispose to cholelithiasis.

None of the choleretic or cholagogue drugs are contra-indicated in pregnancy, and the following are discussed in this chapter:

	Recommendation	Page
Dehydrocholic acid	NC	34
Chenodesoxycholic acid	P	35
Imechrome	NC	36
Camphamyl	NC	36
Cyclovalone	NC	37
Cinarine	NC	37
Hexiprobene	NC	38
Fencibutyrol	NC	38
Hydroxybutyl oxide	NC	38
Menbutone	NC	39
Propylbenzene	NC	39
Sorbitol	NC	39

We believe that there is insufficient information on the following drugs to make any recommendation on their use in pregnancy: boldine, cyclobutyrol, hexacyprone, phenipentol, florantirone, extract of cholecystic wall, sodium dimethocinnamate (page 40).

Dehydrocholic acid

(MW 402.5)

Not contra-indicated in pregnancy.

Dehydrocholic acid is a semi-synthetic derivative of cholic acid, and is present in the bile, both free and conjugated with glycine or taurine. It has an

emulsifying action on lipids, as well as stimulating pancreatic secretion, activating pancreatic lipase, and functioning as a hydrocholeretic. Dehydrocholic acid thus increases bile volume as well as the amounts of solutes in bile. It improves hepatic arterial flow and intestinal motility, but diminishes bilirubin excretion. Dehydrocholic acid is used to stimulate digestion and is also given intravenously as a diagnostic aid to measure circulation time.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and this has been confirmed by the manufacturer [1].

No experimental studies have been described on the use of dehydrocholic acid in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta Albert-Farma - Milano.

Chenodesoxycholic acid

Chendol, $3\alpha, 7\alpha$ -dihydroxy- 5β -cholan-24-oic acid (MW 392.6)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic		P	P		

To be used with care in pregnancy.

Chenodesoxycholic acid is a synthetic derivative of the bile acids. When eliminated in the bile, it is transformed by intestinal flora into lithocholic acid. If the latter is not conjugated, it enters the enterohepatic circulation, and can cause liver damage. Chenodesoxycholic acid is also converted into its epimer, ursochenodesoxycholic acid, which is not hepatotoxic, but is therapeutically active and has minor side effects. In man, in contrast to the Rhesus monkey, excretion of lithocholic acid and its metabolism to ursochenodesoxycholic acid is efficient, and thus liver damage, as assessed by increase in SGOT and SGPT, is slight and transitory. The mechanism of action of chenodesoxycholic acid is controversial. It has, however, been shown to reduce the biliary concentration of cholesterol, thus diminishing the possibility of stone formation. Chenodesoxycholic acid also lowers plasma triglyceride levels, but not those of cholesterol. It also favours choleresis and intestinal motility, as does dehydrocholic acid (see page 34). Chenodesoxycholic acid is used to reduce the volume of radio-transparent biliary calculi (complete disappearance is exceptional). This requires many months, and often more than one year, of treatment, and the success rate varies between 50 and 60%. Chenodesoxycholic acid is also used in the therapy of hypertriglyceridaemia.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. The use of chenodesoxycholic acid is, however,

contra-indicated on the basis of experimental data [1], since the foetus probably is less efficient than the adult at detoxifying drugs. We advise care in its use in pregnancy.

In the Rhesus monkey, an oral dose of 60–120 mg/kg from the 21st to the 45th day of pregnancy caused hepato-cellular necrosis, tico-renal necrosis, and renal interstitial haemorrhage in the foetus, which was born by caesarian section on the 120th day (normal pregnancy lasts 266 days). No macroscopic or skeletal lesions were seen, and foetal and placental weights were normal [1, 2].

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- [2] Palmer A.K., Heywood R.: *Toxicology* 2, 239, 1974.

Imechrome

hydroxy-7-methyl-4-oxo-2-benzopyran-2H-1 (MW 176.16)

Not contra-indicated in pregnancy.

Imechrome is a methyl-umbeliferone, similar to the natural product found in essential oils. Pharmacological investigation has demonstrated that the drug processes choleric and antispastic actions on the sphincter of Oddi, as well as on the gall bladder and on smooth muscle in general [2].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3].

In the rat, transplacental passage of imechrome has been demonstrated [1]. Oral doses of 50–200–1200 mg/kg (the therapeutic dose is 20 mg/kg) from the 6th to the 15th day of pregnancy were neither embryofoetotoxic nor teratogenic [1, 2]. In the mouse, doses of 50–200–800 mg/kg 15 days before mating were without harmful effects [1], and similar doses in the rabbit from the 6th to the 15th day of pregnancy were neither foetotoxic nor teratogenic [1].

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- [2] Taddei I.: *Sperimentazione farmacologica del preparato LM 94* - Istituto di Farmacologia - Università di Siena, 1967. Comunicazione personale della Ditta Formenti - Milano.
- [3] *Dictionaire Vidal* - O.V.P. Ed; - Paris, 1975.

Camphamyl

sodium salt of the phenyl-*n*-amylmonoester of camphoric acid (MW 368.5)

Not contra-indicated in pregnancy.

Camphamyl is a synthetic drug with a mainly antispastic action on the bile and choleric ducts.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat and rabbit, camphamyl was neither embryofoetotoxic nor teratogenic [1]. In the rat, oral doses of 25–100 mg/kg from the 7th to the 16th day of pregnancy did not affect the course of pregnancy, and were without side effects [1]. In the rabbit, oral doses of 20–200 mg/kg from the 7th to the 19th day of pregnancy gave similar results, although an abortion was verified in one case [1].

Bibliography

- [1] Comunicazione personale della Ditta Zambelletti - Milano.

Cyclovalone

2,6-divanilylidene-cyclohexanone (MW 366.4)

Not contra-indicated in pregnancy.

Cyclovalone is a synthetic drug with choleretic and cholagogue action.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers have confirmed this [1].

No experimental studies have been described on the use of cyclovalone in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Roger-Bellon - Sesto San Giovanni.

Cinarine

dicafeic ester of quinic acid (MW 516.44)

Not contra-indicated in pregnancy.

Cinarine is a synthetic drug with a choleretic action.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the mouse, rat, rabbit, and chick embryo, cinarine was neither embryo-foetotoxic nor teratogenic [1]. In the mouse, oral doses of 300 mg/kg (50 times therapeutic) throughout pregnancy were without harmful effects [1]. In the rat, oral doses of 10–30–60–300 mg/kg from the 5th to the 15th day of pregnancy did not induce abortion, and were without harmful effects [1]. In the rabbit, oral doses of 150–300–500 mg/kg from the 6th to the 16th day of pregnancy were not teratogenic [1]. In chick embryo, a dose of 12.5–25 mg injected into the yolk sac did not affect the incidence of malformations compared to a control group [1]. The authors conclude that cinarine, even at high doses, is not teratogenic in the species studied.

Bibliography

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Hexiprobene

sodium 2-(2-hydroxy-3*n*-hexyloxy-propoxy)-benzoate (MW 318.35)

Not contra-indicated in pregnancy.

Hexiprobene is a choleretic which increases elimination of bilirubin and of cholesterol. It is partially inactivated by glucuronyl conjugation.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and this has been confirmed by the manufacturers [1].

In the mouse, rat, and rabbit, hexiprobene was neither foetotoxic nor teratogenic [2]. Doses of 100–200 mg/kg/day in the mouse, 250–500 mg/kg/day in the rat, and 150 mg/kg/day in the rabbit were without harmful effects [2].

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Fencibutyrol

α -(1-hydroxy-4-phenylcyclohexyl)butyric acid (MW 262.34)

Not contra-indicated in pregnancy.

Fencibutyrol is a synthetic drug with antispastic and choleretic actions on the biliary duct.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and this has been confirmed by the manufacturers [1].

No experimental studies have been described on the use of fencibutyrol in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Maggioni - Milano.

Hydroxybutyl oxide

(MW 155.26)

Not contra-indicated in pregnancy.

Hydroxybutyl oxide or dihydroxydibutyl ether is a drug with choleretic and antispastic actions on the bile duct.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy.

In the rabbit, oral doses of 300 mg/kg (therapeutic dose) from the 7th to the 15th day of pregnancy did not affect foetal development or cause malformations [1].

Bibliography

- [1] Felisati D.: *Tossicità gravidica e fetale del diidrossidibutilettere* - Comunicazione personale della Ditta Lusofarmaco - Milano.

Menbutone

1-methoxy-4-naphthoylpropionic acid (MW 258.29)

Not contra-indicated in pregnancy.

Menbutone is a synthetic drug with choleretic and cholagogue actions.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of menbutone in pregnancy in laboratory animals.

Bibliography

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- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
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Propylbenzene

1-phenylpropanol (MW 136.21)

Not contra-indicated in pregnancy.

Propylbenzene has a choleretic action.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been found on the use of propylbenzene in pregnancy in laboratory animals.

Bibliography

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Sorbitol

(MW 182.0)

Not contra-indicated in pregnancy.

Sorbitol is a poly-alcohol largely used in gastroenterology, completely atoxic and slightly absorbed from the digestive tract. It possesses a laxative effect, as a result of an osmotic mechanism. It has a kinetic effect on the bile duct and on the intestinal taenia, mediated by the production of cholecystokinin and villikinin.

The use of sorbitol in pregnancy is not contra-indicated, because of its very low toxicity. It has in fact been used with excellent results in the therapy of hyperemesis gravidarum in the first and second trimesters — it abolishes the emetic reflex [1]. Sorbitol is also used to produce dyskinesia of the biliary tract after cholecystectomy [2] without side effects in the mother or the foetus.

In the rat and mouse, sorbitol, even when associated with prozapine, is neither embryofetotoxic nor teratogenic [3].

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Boldine

(MW 327.37)

Boldine, an alkaloid from *Boldus molina*, has a hydrocholeretic action, that is, it modifies the physical and chemical characteristics of bile, making it less viscous and more fluid. It also has a slight laxative and diuretic effect.

Cyclobutyrol

α -(hydroxycyclohexyl)-butyrate of sodium (MW 186.24)

Cyclobutyrol is a synthetic drug with 'true' choleretic action, that is, it stimulates the production of bile and not just its volume.

Hexacyprone

calcium salts of 2-benzylcyclohexanone-2- β -propionic acid (MW 260.18)

Hexacyprone is a synthetic choleretic with a slight cholagogue action.

Phenipentol

1-phenyl-1-hydroxy-*n*-pentane (MW 164.27)

Phenipentol is a synthetic choleretic.

Florantirone

γ -oxo-8-fluoranthenebutyric acid (MW 302.31)

Florantirone is a synthetic hydrocholeretic analogous to dehydrocholic acid, although it produces greater elimination of bile salts.

Extract of cholecystic wall

Extract of bovine cholecystic wall has been shown experimentally to have a clarifying action on plasma, analogous to that of heparin and of cholesterol-reducing substances.

Sodium dimethocinnamate

sodium 3,4-dimethoxycinnamate (MW 230.22)

Dimethocinnamate is a synthetic choleretic.

We have been unable to find information in the use of these drugs in pregnancy, either in the literature or from the manufacturers. Although no harmful effects have been reported, we advise against their use in pregnancy or in women of childbearing age who are likely to conceive.

5. HEPATOPROTECTORS

This word 'hepatoprotector' is generally used to indicate those substances which are believed to 'protect' the liver from intoxication. Demonstration of their efficiency has often been obtained only experimentally. In this chapter, we omit the so-called 'lipotropic factor' (methionine, choline, inositol, lipocaic) and some vitamins which are treated in the chapter on drugs active on intermediate metabolism (see page 227). Therapy with 'liver extract', with the object of supplying factors which are lacking in the liver, has been much discussed, and could have value only in some forms of anaemia.

None of the hepatoprotectors is contra-indicated in pregnancy, and the following are discussed in this chapter:

	Recommendation	Page
Silimarine	NC	42
Thiopronine	NC	43
Citolone	NC	43
Orazamide	NC	44

We believe that there is insufficient information available on the use of the following drugs in pregnancy to advise on their use: cycloxilic acid, nicotinyl-methylamide, metocalcone, oxybromonaphthoic acid, azintamide, tolinol (page 44-45).

Silimarine

7-chromanol-3'-methyltaxifoline (MW 516.4)

Not contra-indicated in pregnancy.

Silimarine is an antihepatotoxic substance extracted from *Silydum marianum*, a medicinal plant known for many years. Its hepatoprotective action has been demonstrated in cases of poisoning by *Amanita phalloides* [2], by thioacetamide [3], and by carbon tetrachloride [4].

No harmful effects have been reported on the human foetus, the mother, or the pregnancy [5].

In the rat, silimarine administered orally at doses of 1 g/kg/day from the 16th to the 18th day of pregnancy was neither embryofoetotoxic nor teratogenic [1]. In the rabbit, oral doses of 100 mg/kg/day from the 8th to the 17th day of pregnancy were without harmful effects [1].

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Thiopronine

α -mercapto-propionylglycine (MW 116.21)

Not contra-indicated in pregnancy.

Mercapto-propionylglycine is a donor of labile sulphhydryl groups which are essential to the activity of numerous enzymes and of insulin. It therefore exerts a protective and detoxicating action, by activating processes of conjugation of both endogenous and exogenous substances. Experimentally, this has been proved, for example, in intoxication due to heavy metals and alcohol.

Thiopronine has been used in the treatment of hyperemesis [4] and of gestosis in the third trimester [1, 4], particularly where there is liver damage [2]. No side effects in the foetus, the pregnancy, or the neonate were noted [2], and normalization of blood lipids was obtained [1], as well as restoration of normal transaminase levels [2].

In the rabbit, thiopronine was not foetotoxic [3].

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Citolone

2-acetamido-4-mercaptoputyric acid γ -thiolactone (MW 159.2)

Not contra-indicated in pregnancy.

Acetylhomocysteine thiolactone, a donor of sulphhydryl groups, has a protective action on liver lesions induced experimentally by bromobenzene, allyl alcohol, or carbon tetrachloride. Although not reducing liver content of lipids, citolone prevents the development of hepatic fibrosis by diminishing their co-enzyme A content and by reduction of glutathione.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and this has been confirmed by the manufacturer [1].

In the rat and rabbit, citolone was not teratogenic [1].

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Orazamide

4-amino-5-carbamido-imidazole-2,4-dihydroxy-6-pyrimidine carbonate
(MW 318.26)

Not contra-indicated in pregnancy.

Orazamide is a synthetic drug which stimulates hepatic regeneration.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, mouse, and rabbit, orazamide was without harmful effects [1, 2, 3]. In the rat, oral doses of 200–400–500 mg/kg from the 9th to the 15th day of pregnancy were neither embryofoetotoxic nor teratogenic [1]. Oral doses of 125–250 mg/kg from the 1st to the 16th day of gestation were likewise without harmful effects in the mother and the foetus [2]. In the mouse, oral doses of 400–1000 mg/kg from the 7th to the 13th day of pregnancy were neither embryofoetotoxic nor teratogenic [3]. In the rabbit, oral doses of 125–250 mg/kg from the 6th to the 25th day of pregnancy did not affect the course of pregnancy or produce side effects in the foetus [2].

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* * * * *

Cycloxylic acid

2-hydroxy-*trans*-2-phenyl-cyclohexanecarboxylic acid (MW 220.29)

Nicotinylmethyleamide

N-oxymethyl-nicotinamide (MW 152.15)

This drug associates the metabolic action of nicotinamide, particularly on lipid metabolism (see nicotinamide, page 253) with an antiseptic action in the intestine and in the bile duct, and diminished production of ammonia. Possible risks of loss of labile methyl groups which follow the administration of nicotinamide are avoided.

Metocalcone

1, 2, 4-trimethoxychalcone (MW 298.32)

Oxybromonaphthoic acid

bromo-hydroxynaphthoic acid (MW 267.09)

Azintamide

3-chloro-pyridazine-6-mercapto-acetic acid diethylamide (MW 259.77)

Tolinol

p-tolylmethylcarbinol (MW 136.21)

We have been unable to obtain information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. Although there have been no reports of harmful effects, we would advise against their use in pregnancy and in women of childbearing age who are likely to conceive.

6. LAXATIVES AND REGULATORS OF GASTROINTESTINAL MOTILITY

Laxatives are indicated in the therapy of constipation of a functional nature, when suitable dietetic regimens are not effective. Some laxatives are anthraquinone derivatives, such as senna, cascara, and aloin. Others act by an analogous mechanism, coupled with enterohepatic recirculation (phenolphthalein, phenolphthalol), while still others are not absorbed but act by contact (sodium picosulphate). Some are slowly absorbed, and act by an osmotic mechanism (lactose). In this chapter are also included two synthetic products (trimebutine and metoclopramide), which modulate and normalize gastrointestinal peristalsis, the first acting on the the plexuses of Auerbach and Meissner, the second on enkephalic trunks, without affecting the autonomic nervous system. The drugs which modify motility of the gastrointestinal tract, by interfering with this system, are treated in the corresponding chapter (see page 52).

None of the laxatives is contra-indicated in pregnancy, and the following are discussed in this chapter:

	Recommendation	Page
<i>Laxatives</i>		
Glucofrangulin	NC (C during lactation)	46
Senna	NC	47
Aloin	NC (P during lactation)	48
Bisacodyl	NC	48
Cascara	NC (P during lactation)	49
Phenolphthalein	NC	49
Phenolphthalol	NC	50
Sodium picosulphate	NC	50
Lactulose	NC	51
Psyllium	NC	51
<i>Regulators of motility</i>		
Trimebutine	NC	52
Metoclopramide	NC	52

We believe that there is insufficient evidence to recommend the use of bisoxatin in pregnancy (page 54).

6.1 Laxatives

Glucofrangulin

(MW 578.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					C
Chronic					

Not contra-indicated in pregnancy, but is contra-indicated during lactation.

Glucofrangulin (rhamnoglucoside of emodin) is the most important component of the extract of dried bark of the plant *Rhamnus frangula*, and it has purgative properties similar to those of cascara (see page 49).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1], and our own experience supports this.

The passage of glucofrangulin into breast milk has been established. It may cause an increase in gastric motility in the infant [2], and it is therefore preferable to avoid its use during lactation.

No experimental studies have been described on the use of glucofrangulin in pregnancy in laboratory animals.

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Senna

Senokot

Not contra-indicated in pregnancy.

Senna is a galenical preparation obtained from the leaves of *Cassia*, and contains sennosides [1, 2]. In the intestine, these are hydrolyzed with the liberation of anthraquinones which have an irritant action, and are therefore purgative and cause pelvic congestion.

Senna has been used in pregnancy without embryofetotoxic or teratogenic effects [3, 4], and it does not affect the course of pregnancy adversely.

Passage of senna into breast milk has not been demonstrated [5]. According to some authors, traces have been found in the milk [6], while others maintain that it is absent [8]. However, there are no effects in the infant at therapeutic doses [7].

No experimental studies have been found on the use of senna in pregnancy in laboratory animals.

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Aloin

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					P
Chronic					

Not contra-indicated in pregnancy, but should be used with care during lactation.

Aloin consists of a mixture of anthraquinone glycosides which have an irritant action, and are thus purgatives, as well as causing pelvic congestion [1]. At one time, it was erroneously believed that they also had a cholagogue and abortifacient action.

No references to the avoidance of aloin in pregnancy have been found, and therefore it may be prescribed in normal therapeutic doses [2,3]. The manufacturers concur with this view [9].

Anthraquinone glucosides can be secreted in breast milk, and might thus have a purgative effect in the infant [4,5,6,7,10]. However, none of these studies advises against the use of aloin during lactation [5], and we would only suggest that care should be exercised.

No experimental studies have been found on the use of aloin in pregnancy in laboratory animals.

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Bisacodyl

Dulcolax, (4,4'-diacetoxy-diphenyl)-(pyridyl-2)-methane (MW 361.4)

Not contra-indicated in pregnancy.

Bisacodyl is a drug with a phenolphthalein-type structure, and has always been described as a contact laxative, even though its true mechanism of action

is still unknown. It is not absorbed by the intestinal mucosa, and is therefore harmless in pregnancy.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3], and our experience confirms this.

No experimental studies have been described on the use of bisacodyl in pregnancy in laboratory animals.

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Cascara

Cascara sagrada

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					C
Chronic					

Not contra-indicated in pregnancy, but should be used with care during lactation.

Cascara is a complex of anthraquinone glycosides which are hydrolyzed and activated in the colon, where their irritant action takes place, resulting in purging.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

Anthraquinone glycosides may pass into breast milk, and increase gastro-intestinal motility in the infant [1, 2, 4, 5, 6, 7]. Their use is therefore not recommended during lactation.

No experimental studies have been described on the use of cascara in pregnancy in laboratory animals.

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Phenolphthalein

Agarol, Alophen, Petrolagar, Veracolate (MW 318.31)

Not contra-indicated in pregnancy.

Phenolphthalein has a mechanism of action which is similar to that of the

anthraquinones (intestinal motor excitatory action). It is partly absorbed in the intestine (colon), and is slowly excreted with the bile, thus causing purgative effects for 3–4 days after administration. Because of this, accumulation of the drug may occur with continuous administration.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

After administration of 30–60–90 mg/day during the puerperium, no significant amounts of phenolphthalein were found in breast milk [1, 2].

No experimental studies have been described on the use of phenolphthalein in pregnancy in laboratory animals.

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Phenolphthalol

Normolax, bis-(oxyphenyl)methylbenzylic alcohol (MW 306.3)

Not contra-indicated in pregnancy.

Phenolphthalol is an analogue of phenolphthalein, and it has the same pharmacological properties (see page 49).

Phenolphthalol has been used in pregnancy with no side effects in the foetus or the mother [1].

When used in the puerperium, phenolphthalol has no harmful effects in the infant, since it does not pass into breast milk [2].

In the rat, at a dose of five times therapeutic orally from the 1st to the 17th day of pregnancy, phenolphthalein did not affect the course of pregnancy, provoke abortions, or induce malformations [2].

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Sodium picosulphate

4,4'-(2-picolydene)-bis-phenyl-sulphuric acid disodium salt (MW 362.31)

Not contra-indicated in pregnancy.

Sodium picosulphate is a derivative of diphenylmethane, and is only very slightly absorbed from the intestinal tract, since it is not readily hydrolyzed. Absence of absorption excludes the possibility of foetal damage.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2]. The manufacturers agree with this view [1], and our own experience is similar. In 30 patients at various stages of pregnancy, 6–25 drops of sodium picosulphate were administered for a maximum period of 20 days without embryofetotoxic or teratogenic effects [2].

Sodium picosulphate passes into breast milk, but does not affect milk secretion [3].

No experimental studies have been described on the use of sodium picosulphate in pregnancy in laboratory animals.

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Lactulose

Dulphalac, Gatinar, D-galactopyranosyl-D-fructose (MW 342.3)

Not contra-indicated in pregnancy.

Lactulose is a glycide which is not immediately absorbed from the digestive tract. It thus has a mild action as an osmotic purgative, and acts as a substrate for the development of intestinal flora of the fermentative type, but not the ammoniogenetic or putrefactive types. In the presence of diminished hepatic deamination, lactulose may produce a cerebral toxic syndrome, even leading to a hyperammonaemic coma.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2], and the manufacturers have confirmed this [3].

No experimental studies have been described on the use of lactulose in pregnancy in laboratory animals.

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Psyllium

Metamucil, purified mucilage of *Plantago ovata* Forsk

Not contra-indicated in pregnancy.

The active substance in psyllium is a polysaccharide which is not digested by pancreatic juices, but is partially attacked by intestinal bacterial flora. It is obtained from the cortex of the psyllium seed, and consists of a branched pentose chain, principally xylose. Psyllium is defined as a mass hydrophylic agent capable of fixing large quantities of water. During its passage through the intestine, it forms a voluminous colloidal mass which stimulates peristalsis in a physiological manner. The faeces become soft, and are evacuated easily, diminishing the effort necessary for defaecation. This has notable advantages in haemorrhoidal congestion, and in ano-rectal lesions. Ingested before meals, psyllium fills the stomach with a non-digestible mass, thus contributing to a reduction in appetite.

Psyllium may be used at any stage of pregnancy or lactation, because it is non-digestible and non-absorbable. The manufacturers concur with this view [1].

No experimental studies have been found on the use of psyllium in pregnancy in laboratory animals.

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6.2 Regulators of motility

Trimebutine

maleate of the

3, 4, 5-trimethoxybenzoic ester of phenyl-2-dimethylamino-2-*n*-butanol (MW 503.59)

Not contra-indicated in pregnancy.

Trimebutine is a modulator of gastrointestinal peristalsis, and improves gut transit time. It acts on the plexuses of Auerbach and of Meissner, and has no central or atropine-like effects. Trimebutine is almost free of side effects, and is used in the treatment of dyskinesia of the digestive tract and in radio-diagnostics, to facilitate passage through the pylorus of the opaque enema. It is also used in surgery to facilitate post-operative recovery of intestinal motility. Trimebutine diminishes nausea and vomiting, which can be troublesome in pregnancy.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers have confirmed this [1].

In the rat and rabbit, trimebutine was neither embryofetotoxic nor teratogenic [1]. In the rat, oral doses of 25–125 mg/kg and intramuscular doses of 2–5 mg/kg from the 3rd to the 17th day of pregnancy were without harmful effects [1]. In the rabbit, oral doses of 25 mg/kg or intravenous doses of 5 mg/kg from the 3rd to the 23rd day of pregnancy did not adversely affect the mother or the foetus [1].

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Metoclopramide

Primperan, 2-methoxy-5-chloro-*N*-diethylaminoethylbenzimidate (MW 299.81)

Not contra-indicated in pregnancy.

Metoclopramide is a synthetic drug which is completely different from drugs commonly used in disturbances of the gastrointestinal tract, such as the parasympatholytics, the neuroleptics, and the ganglion blockers. The pharmacodynamic properties of this drug may be summarized as follows: (a) it does not have vagolytic, antihistamine, or sedative effects; (b) it acts on centres in the encephalic trunk which control motility of the digestive tract; (c) its action is

characterized by a combination of dilatation and of gastro-duodenal-jejunal hyperkinesia, with a decrease in transit time. Metoclopramide can cause diarrhoea, constipation, anxiety, and extrapyramidal disturbances (dyskinesia, tremors), particularly when administered in association with phenothiazines. An increase of 3–8 times the normal amount of prolactin has been reported, for which reason, its use in prolactin-dependent mammary carcinoma is not advised. It rarely gives rise to the appearance of galactorrhoea.

Metoclopramide administered in pregnancy as an anti-emetic is free from embryofetotoxic or teratogenic effects. The side effects in the mother are similar to those previously described [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. Recently, its use in the first trimester has been opposed [20], even although the hyperprolactinaemic effect does not constitute a contra-indication, since an increase in this hormone is normal in pregnancy. Metoclopramide is used in the treatment of hypogalactia [21].

Ninety patients with hyperemesis gravidarum (70 in the first trimester and 20 in the second and third) were treated with metoclopramide at oral doses of 10–40 mg/day and intravenously with 30 mg/day (in serious cases). No embryofetotoxic or teratogenic effects were reported [2]. Of 21 patients treated for hyperemesis during pregnancy in the first trimester with oral doses of 20 mg/day for 5 days, six gave birth to healthy infants of normal weight, one had an abortion because of uterine malformation, and in the others, pregnancy proceeded normally [3]. A further four patients treated with 30–40 mg/day for 6–7 days gave birth to healthy offspring of normal weight [3]. In 20 women with hyperemesis, administration of metoclopramide at a dose of 40 mg/day until the symptoms resolved caused no side effects in the mother or the foetus [4]. Administration of oral, intravenous, or intramuscular doses of 20–30 mg/day to 27 patients with hyperemesis (18 in the first trimester, 9 in the second) was without harmful effects [5]. In 22 patients, administration of the drug at various stages of pregnancy in oral doses of 30 mg/day or parenteral doses of 20 mg/day was without side effects in the foetus [6]. Administered to 28 patients at various stages of pregnancy at doses of 40 mg/day parenterally for 3–4 days, metoclopramide was not teratogenic [7]. Administration of the drug in the first 28 weeks of pregnancy at a dose of 30 mg/day for about 7 days was not teratogenic [1].

In the rat, mouse, and rabbit, metoclopramide was neither embryofetotoxic nor teratogenic [8, 9, 14]. In all three species, treated from the 7th to the 12th, the 9th to the 14th, and the 8th to the 16th days of pregnancy respectively with doses of 10–200 mg/kg (50–60 mg/day), the drug had no harmful effects [8]. In the mouse and rat, doses of 1.5–10 mg/kg, and in the rabbit, doses of 12–20 mg/kg, were likewise without side effects [9].

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Bisoxatin

2-bis(4-acetoxy)-phenyl-2,3-dihydro-1,4-benzoxazin-3-one (MW 333.15)

We have been unable to find any information on the use of this drug in pregnancy, either in the literature or from the manufacturers. Although there are no reports of harmful effects, we believe that in the absence of sufficient information, this drug should be avoided if possible in pregnancy, and in women of childbearing age who are likely to conceive.

Part 5

Drugs active on the bronchopulmonary tract

	Page
1. Expectorants	56
2. Cough suppressants	60

1. EXPECTORANTS

The expectorants are drugs which have a fluidizing action on bronchial secretions. Some, such as acetylcysteine, are mucolytics. Others act by an enzymatic mechanism (trypsin, cymotrypsin, etc.) and are classified amongst the enzymes (see page 274). The following drugs are discussed in this chapter:

	Recommendation	Page
Acetylcysteine	NC	56
Methylcysteine hydrochloride	NC	57
Bromhexine hydrochloride	NC	57
Guaiphenesin	NC	58
Sobrerol	NC	58
Sulphoguaiacol	NC	59

None of these drugs is contra-indicated in pregnancy.

Acetylcysteine

Airbron, 1- α -acetamido- β -mercaptopropionic acid (MW 163.2)

Not contra-indicated in pregnancy.

Acetylcysteine is a derivative of cysteine with a fluidizing action on mucus and mucopurulent secretions. Its action consists of a depolymerization of mucoprotein complexes and of DNA, which give viscosity to sputum. The properties of acetylcysteine cause it to be used mainly in bronchopulmonary infection.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

In the rat, mouse, and rabbit, acetylcysteine was essentially without harmful effects in pregnancy [5, 6], although at high doses, foetotoxic effects have been observed. In the rat, intramuscular doses of 31–125 mg/kg from the 7th to the 20th day of pregnancy, given in association with thiamphenicol, caused an increase in foetal resorptions, a reduction of foetal weight, and malformations of the kidney and diaphragm [5]. Intraperitoneal doses of 25–50 mg/kg from the 9th to the 14th day of pregnancy were neither embryofoetotoxic nor teratogenic. At higher doses, up to 100 mg, acetylcysteine caused delay in bone formation, and 70% resorptions, but there were no malformations [6].

In the mouse, intramuscular doses of 62.5–250 mg/kg from the 6th to the 18th day of pregnancy, in association with thiamphenicol, were foetotoxic but not teratogenic [5]. Intraperitoneal doses of 30 mg/kg from the 7th to the 12th day of pregnancy were neither embryofoetotoxic nor teratogenic. At higher

doses, up to 700 mg, acetylcysteine caused delay in bone formation and slowed intra-uterine development. No malformations were observed [6].

In the rabbit, acetylcysteine in association with thiamphenicol at intramuscular doses of 16–32–64 mg/kg from the 7th to the 28th day of pregnancy was embryofoetotoxic (increase in resorptions, and decrease in foetal weight) but not teratogenic [5].

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- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
- [3] Massam D.: *A.B.P.I. Data Sheet Compendium* - Butler & Tanner Ed. - London, 1975.
- [4] *Rote List* - Cantor Ed. - Aulendorf, 1975.
- [5] Comunicazione personale della Ditta Zambon - Milano.
- [6] Suzuki Y.: *J. Appl. Pharmacol.* 7, 859, 1973.

Methylcysteine hydrochloride or mecysteine

cysteine methyl ester hydrochloride (MW 171.6)

Not contra-indicated in pregnancy.

Inflammation of the respiratory tract leads to a loss of sulphur in the mucosal secretions. Administration of methylcysteine corrects this loss, and re-establishes the trophism of the muciparous cells in the rhinopharynx. Methylcysteine is metabolized in the same way as cysteine, has a bacteriostatic action, and is used in the therapy of chronic rhinorrhoea, sinusitis, laryngitis, and bronchitis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4], and the manufacturers have confirmed this [5].

No experimental studies have been described on the use of methylcysteine in pregnancy in laboratory animals.

Bibliography

- [1] Kastrup E.K., Schwach E.H.: *Facts and Comparison* - Facts and Comparison Ed. - St. Louis, 1975.
- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
- [3] Massam D.: *A.B.P.I. Data Sheet Compendium* - Butler & Tanner Ed. - London, 1975.
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- [5] Comunicazione personale della Ditta Laboratoires Joullié - Puteaux.

Bromhexine hydrochloride

Alupent, Bisolvomycin, Bisolvon,

N-cyclohexyl-*N*-methyl-(2-amino-3, 5-dibromobenzyl)-amine hydrochloride (MW 412.6)

Not contra-indicated in pregnancy.

Bromhexine has a fluidizing action on bronchial secretions, and is an analgesic, antipyretic, and anti-inflammatory.

No embryofoetotoxic or teratogenic effects have been reported in the human foetus, and the manufacturers have confirmed this [1].

In the mouse and rat, bromhexine had no toxic or teratogenic effects [2]. Oral doses of 99–165–231 mg/kg from the 6th to the 16th day of pregnancy did not affect the number, the weight, or the size of the foetuses, or the number of foetal resorptions [2].

Bibliography

- [1] Comunicazione personale della Ditta Boehringer Ingelheim - Firenze.
- [2] Scarinci F.: *Relazione sul Tetra Abiadin* - Istituto di Farmacologia - Università di Urbino, 1973.

Guiaphenesin or guaiacol glyceryl ether

Bricanyl, Dimotane, Exyphen, Pulmodrine, Robitussin,
3-(*o*-methoxyphenoxy)-propan-1, 2-diol (MW 198.2)

Not contra-indicated in pregnancy.

Guiaphenesin reduces the viscosity of the sputum, and at high doses it has a muscle relaxant action (skeletal muscle) similar to that of mephenesin (see Vol. 1). It also reduces platelet adhesiveness.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of guiaphenesin in pregnancy in laboratory animals. The manufacturers also state that they are unaware of any such studies [4].

Bibliography

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- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
- [3] Massam D.: *A. B. P. I. Data Sheet Compendium* - Butler & Tanner Ed. - London, 1975.
- [4] Comunicazione personale della Ditta Ciba - Saronno.

Sobrerol

1-methyl- α -hydroxy-isopropyl-cyclohexenol-6 (MW 170.3)

Not contra-indicated in pregnancy.

Sobrerol has a fluidizing action on bronchial secretions and increases vital capacity and pulmonary ventilation.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy, and information from the manufacturers supports this [1].

In the rat, mouse, and rabbit, sobrerol was neither embryofoetotoxic nor teratogenic [2]. In the rat, subcutaneous doses of 75–125 mg/kg from the 1st to the 21st day of pregnancy were without harmful effects [2]. In the mouse, similar doses from the 1st to the 19th day of pregnancy, and in the rabbit, doses of 25–50 mg/kg from the 8th to the 16th day of pregnancy were likewise without side effects [2].

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- [1] Comunicazione personale della Ditta Corvi - Piacenza.
- [2] Scuri R., Valdecchi B., Riboni R., Dalla Valle V., Cellari C.: *Atti Accad. Med. Lombarda* 29, 31, 1974.

Sulphoguiacol

3-hydroxy-2(o 4)-methoxybenzenesulphonate of potassium (MW 242.3)

Not contra-indicated in pregnancy.

Guiacol, a methyl ester of pyrocatechin, is the principal component of the creosote prepared from the beech tree, formerly used in the treatment of bronchopulmonary illness because of its mild stimulant and antibacterial action on the mucosa of the respiratory tract. Some derivatives are better tolerated orally than guiacol itself.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of sulphoguiacol in pregnancy in laboratory animals.

Bibliography

- [1] Kastrup E.K., Schwach E.H.: *Facts and Comparison* - Facts and Comparison Ed. - St. Louis, 1975.
- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
- [3] Massam D.: *A.B.P.I. Data Sheet Compendium* - Butler & Tanner Ed. - London, 1975.

2. COUGH SUPPRESSANTS

Cough suppressants are represented here by certain opium alkaloids and their derivatives (partly described among the narcotic analgesics, Vol. 1), and by numerous synthetic products. In the first category are codeine and dihydrocodeinone, which have a central depressant action like that of morphine, and dextromethorphan, noscapine, and thebaine, which do not. The synthetic products are central cough suppressants, or they may act on peripheral receptors where the cough reflex originates. They are almost free from sedative and depressant effects on the respiratory centre. Some of them also reduce secretions (carbetapentane) or are anti-inflammatory (oxolamine). The following drugs are discussed here:

	Recommendation	Page
<i>Opium alkaloids and their derivatives</i>		
Codeine phosphate	NC (P before parturition)	61
Dihydrocodeinone bitartrate	NC (P before parturition)	62
Dextromethorphan hydrochloride	NC	62
Noscapine hydrochloride	NC	63
Thebaine	NC	63
<i>Synthetic products</i>		
Benzonatate	NC	64
Butamirate	NC	64
Carbetapentane citrate	NC	65
Clobutinol hydrochloride	NC	65
Clofedanol hydrochloride	NC	65
Demethoxanate hydrochloride	NC	66
Dropropizine	NC	66
Guaiapate acetate	NC	66
Morclophone hydrochloride	NC	67
Oxolamine	NC	67
Pipazetate hydrochloride	NC	68
Promolate	NC	68

None of these drugs is contra-indicated during pregnancy, but the alkaloids with central sedative action, which are depressants of the respiratory centres and analgesics (codeine phosphate and dihydrocodeinone) are not advised towards the end of pregnancy or in labour, as there may be effects on the neonate.

We believe that insufficient information exists on the use of the following drugs in pregnancy to give an opinion: bibenzonium bromide, isoaminile, oxeladime, benproperine, sodium dibunate, naphthocizine, pridinol (see page 68).

A retrospective study [1] has shown that among mothers of malformed infants there was a significantly greater number who had taken antacids, iron preparations, and cough sedatives during pregnancy, compared to a control group. We do not believe that this investigation is reliable, and therefore we do not share the conclusions of the authors.

Bibliography

[1] Nelson M.M., Forfar J.O.: *Brit. Med. J.* 1, 523, 1971.

2.1 Opium alkaloids and their derivatives

Codeine phosphate

methylmorphine phosphate (MW 406.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				P	
Chronic			P		

Not contra-indicated during pregnancy, but should be used with care in the later stages.

Codeine or methylmorphine is an opium alkaloid. It has an analgesic action (1/10th that of morphine), and is a central depressant, acting on the bulbar cough centres. It also reduces the motility and secretions of the digestive tract, and at high doses causes miosis, euphoria, emesis, and peripheral vasodilation following depression of vasomotor centres. Codeine is partly demethylated to morphine. It is potentiated by phenothiazines, by imipramine, and by monoamine oxidase inhibitors.

Codeine does not depress uterine contractility, but prolongs the duration of labour because it makes the patient less able to cooperate. Codeine in therapeutic doses is not contra-indicated in pregnancy [1, 2, 3, 5] or in the puerperium, since it does not pass into breast milk [4]. No reports have been found of embryo-foetotoxic or teratogenic effects, although some authors have reservations regarding its use immediately before labour.

No experimental studies have been described on the use of codeine in pregnancy in laboratory animals.

Bibliography

[1] Kastrup E.K., Schwach E.H.: *Facts and Comparison* - Facts and Comparison Ed. - St. Louis, 1975.

- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
 [3] *Dictionnaire Vidal* - O.V.P. Ed. - Paris, 1975.
 [4] Kwit N.T., Hatcher R.A.: *Am. J. Dis. Child.* 49, 900, 1935.
 [5] Müller W. Chr.: *Münch. Med. Wschr.* 34, 1687, 1969.

Dihydrocodeinone bitartrate or hydrocodone

4,5-epoxy-3-methoxy-*N*-methyl-6-oxomorphinan hydrogen tartrate
 (MW 494.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care in the later stages.

Hydrocodone or dihydrocodeinone is an opium alkaloid with antitussive and analgesic activity.

Dihydrocodeinone crosses the placental barrier, and appears in foetal urine for a few days after birth [1]. Administration of the drug in the last part of pregnancy and shortly before parturition can produce respiratory depression in the neonate, as occurs with other opium alkaloids. There may also be respiratory and metabolic acidosis, which resolves only slowly [1, 2, 5]. In prolonged therapy, there may be a withdrawal syndrome in the neonate which is characterized by psychomotor agitation, shrill crying, difficulty in feeding, diarrhoea, fever, dehydration to the point of convulsions, and crises of apnoea [1, 3, 4].

No experimental studies have been found on the use of dihydrocodeinone in pregnancy in laboratory animals.

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- [1] Reginster L.: *Rev. Méd. de Liège* 21, 473, 1966.
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 [3] Fisch G.R., Henley W.L.: *Pediatrics* 28, 852, 1961 (cit. da 1).
 [4] Desmond M.M., Franklin R.R., Blattner R.J., Hill R.M.: *Ped. Clin. North Am.* 8, 421, 1961.
 [5] Arena J.M.: *Clin. Ped.* 3, 450, 1964.

Dextromethorphan hydrochloride

Benafed, Cosylan, Lotussin, Muflin, Syrtussar,
d-3-methoxy-*N*-methylnorphinan hydrobromide (MW 370.3)

Not contra-indicated in pregnancy.

Dextromethorphan is an isomer of codeine and possesses a central

antitussive action without analgesic effects. It also has no effect on the digestive tract or on respiratory centres.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of dextromethorphan in pregnancy in laboratory animals.

Bibliography

- [1] Kastrup E.K., Schwach E.H.: *Facts and Comparison* - Facts and Comparison Ed. - St. Louis, 1975.
- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
- [3] *Dictionaire Vidal* - O.V.P. Ed. - Paris, 1975.

Noscapine hydrochloride

Extil, Theo-nar, Triotussic,

5-(6,7-dimethoxy-1-oxophthalan-3-yl)-4-methoxy-6-methyl-1,3-dioxolo-(4,5-g)-isoquinoline (MW 413.43)

Not contra-indicated in pregnancy.

Noscapine is an opium alkaloid structurally related to papaverine, with a central antitussive action. It does not cause psychophysical dependence, euphoria, analgesia, or sedation. Like papaverine (Vol. 1), it depresses bronchial and cardiac smooth muscle, but this effect is not present at therapeutic doses.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2, 3, 4, 5], and this has been confirmed by the manufacturers [1].

No experimental studies have been described on the use of noscapine in pregnancy in laboratory animals.

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- [2] Kastrup E.K., Schwach E.H.: *Facts and Comparison* - Facts and Comparison Ed. - St. Louis, 1975.
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- [4] *Dictionaire Vidal* - O.V.P. Ed. - Paris, 1975.
- [5] Massam D.: *A. B. P. I. Data Sheet Compendium* - Butler & Tanner Ed. - London, 1975.

Thebaine

6-acetoxy-4,5-epoxy-3-methoxy-N-methylmorphin-6-ene (MW 341.4)

Not contra-indicated in pregnancy.

Thebaine is a derivative of thebaine, a phenanthrene alkaloid present in opium, with an excitant action on the spinal cord. It thus has a tendency to produce convulsions and tetany. Thebaine, unlike other opium alkaloids, has no analgesic action.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been described on the use of thebacone in pregnancy in laboratory animals.

Bibliography

- [1] *Rote List* - Cantor Ed. - Aulendorf, 1975.

2.2 Synthetic products

Benzonate

p-n-butylamino-benzoate of the monomethyl ether of polyethylene glycol (MW 603.73)

Not contra-indicated in pregnancy.

Benzonate is an synthetic drug which possesses a central sedative action together with a local anaesthetic action on deep receptors of the respiratory tract, which are responsible for the cough stimulus.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers have confirmed this [1].

No experimental studies have been described on the use of benzonate in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Ciba-Geigy - Origgio.

Butamirate

diethyl-aminoethoxyethanol phenyl-ethyl-acetate citrate (MW 301.27)

Not contra-indicated in pregnancy.

Butamirate is a centrally acting cough suppressant.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rabbit and rat, butamirate was neither embryofoetotoxic nor teratogenic [1]. In the rabbit, subcutaneous doses of 25 mg/kg from the 7th to the 15th day of pregnancy, or oral doses of 50 mg/kg for the same period, were without harmful effects [1]. In the rat, subcutaneous doses of 25 mg/kg, or oral doses of 100 mg/kg from the 1st to the 15th day of pregnancy had no side effects on the foetus [1].

Bibliography

- [1] Relazione al Ministero della Sanità dell'Istituto di Farmacologia dell'Università di Milano, 1966 - Comunicazione personale della Ditta Bonomelli-Hommel - Dolzago.

Carbetapentane citrate or pentoxiverine citrate

2-(2-diethylaminoethoxy)ethyl-1-phenylcyclopentane-1-carboxylate dihydrogen citrate (MW 525.6)

Not contra-indicated in pregnancy.

Carbetapentane is a cough suppressant, and also reduces bronchial secretions.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been described on the use of carbetapentane in pregnancy in laboratory animals.

Bibliography

[1] *Dictionaire Vidal* - O.V.P. Ed. - Paris, 1975.

Clobutinol hydrochloride

1-*p*-chlorophenyl-2,3-dimethylamino-butanol(2)hydrochloride (MW 293.15)

Not contra-indicated in pregnancy.

Clobutinol is a centrally acting cough suppressant which improves expectoration and has no hypnotic action.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy.

In the rat, mouse, and rabbit, clobutinol was neither embryofoetotoxic nor teratogenic [1, 2]. In the rabbit, oral doses of 2–5 mg/kg throughout pregnancy did not affect fertility or reproduction, and embryonic and foetal development were normal [1]. In the mouse and rat, oral doses equivalent to 1/20th, 1/10th, and 1/8th LD₅₀ from the 6th to the 16th day of pregnancy were without harmful effects [2].

Bibliography

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[2] Scarinci V.: *Ricerche tossicologiche condotte su un prodotto denominato "Tussilomat" della Ditta Boehringer-Ingelheim* - Firenze, 1973.

Clofedanol hydrochloride

1-phenyl-1-*o*-chlorophenyl-3-dimethylamino-propanol-(1) hydrochloride (MW 326.3)

Not contra-indicated in pregnancy.

Clofedanol is a centrally acting cough suppressant with some peripheral actions.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers confirm this [1], although they have no experimental or clinical data available on the use of clofedanol in pregnancy.

No experimental studies have been described on the use of clofedanol in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta Bayer-Italia - Milano.

Dimethoxanate hydrochloride

2-(2-dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate hydrochloride (MW 394.9)

Not contra-indicated in pregnancy.

Dimethoxanate has a phenothiazine structure, and is a centrally acting cough suppressant with local anaesthetic activity.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, doses of 40 mg/kg for 60 days before parturition did not affect fertility, development of the embryo or the foetus, duration of pregnancy, or the number and weight of the offspring. There were no teratogenic effects [1].

Bibliography

[1] Report 113-002: International Research and Development Corporation Mattawan-Michigan - Comunicazione personale della Ditta Ayerst - Roma.

Dropropizine

3-(4-phenyl-1-piperazinyl)-1, 2-propandiol (MW 236.3)

Not contra-indicated in pregnancy.

Dropropizine is a peripherally acting cough suppressant, and has no central or respiratory depressant activity.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1], and the manufacturers confirm this [2].

No experimental studies have been described on the use of dropropizine in pregnancy in laboratory animals.

Bibliography

[1] *Rote List* - Cantor Ed. - Aulendorf, 1975.

[2] Comunicazione personale della Ditta Formenti - Milano.

Guaiapate acetate

1-(2-methoxyphenoxy)-3, 6-dioxy-8-(N-piperidyl)octane (MW 323.26)

Not contra-indicated in pregnancy.

Guaiapate is a centrally acting cough suppressant, with no effects on the respiratory centres.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of guaiapate in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Maggioni - Milano.

Morclophone hydrochloride

4'-chloro-3,5-dimethoxy-4-(2-morpholino-ethoxy)-benzophenone hydrochloride (MW 442.3)

Not contra-indicated in pregnancy.

Morclophone is a centrally acting cough suppressant, is not narcotic, and has broncholytic properties.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy.

In the rat and rabbit, administration of morclophone in pregnancy was neither embryofetotoxic nor teratogenic [1,2]. In the rat, administration of the drug at oral doses of 15–45 mg/kg/day from the 6th to the 15th day of pregnancy did not cause an increase in foetal resorptions compared to controls, nor were there any teratogenic effects [1]. In the rabbit, administration of oral doses of 5–15–45 mg/kg/day from the 6th to the 18th day of pregnancy did not affect the course of pregnancy or embryogenesis or organogenesis [2].

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Oxolamine

3-phenyl-5-(β -diethylaminoethyl)-1,2,4-oxadiazol (MW 245.32)

Not contra-indicated in pregnancy.

Oxolamine has a peripheral antitussive action and is also anti-inflammatory.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the mouse, rat, and rabbit, oxolamine at doses of 1–10 times therapeutic was not teratogenic [1], but could cause minor bone malformations in the rat [2]. Oral doses of 0.5–5–10 times therapeutic throughout pregnancy had no harmful effects, but 2 mg/day parenterally caused an increase in the number of anomalous vertebrae and centres of ossification in the sternum [2].

In the rabbit, oral doses of 0.5–1–5 times therapeutic from the 1st to the 18th day of pregnancy were not teratogenic [1].

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- [3] Shepard T.H.: *Catalog of teratogenic agents* - The Johns Hopkins University Ed. - Baltimore, 1973.

Pipazetate hydrochloride

thiophenyl-pyridylaminocarbonic acid piperidino-ethoxyethyl ester hydrochloride (MW 436.0)

Not contra-indicated in pregnancy.

Pipazetate is an antitussive with central and peripheral (spasmolytic) mechanisms of action. It does not affect the respiratory centres, nor does it produce habituation.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

In the rat, doses of 200 mg/kg (100 times therapeutic) did not affect foetal development. At higher doses, up to 600 mg/kg (300 times therapeutic), an increase in foetal resorptions was observed [1].

Bibliography

- [1] Comunicazione personale della Ditta Medicamenta - Varese.

Promolate

morpholino-ethyl ester of α -phenoxy-isobutyric acid (MW 293.36)

Not contra-indicated in pregnancy.

Promolate is a synthetic antitussive.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers have not performed any studies of promolate in pregnancy [1].

In the rat, mouse and rabbit, promolate was neither embryofoetotoxic nor teratogenic [2]. In the rat and rabbit, oral doses of 450 mg/kg throughout pregnancy were without harmful effects [2]. In the rabbit, rectal doses of 450 mg/kg from the 8th to the 16th day of pregnancy were not teratogenic [2].

Bibliography

- [1] Comunicazione personale della Ditta Serono - Roma.
- [2] Fischetti B.: *Ricerche farmacologiche e tossicologiche sul composto S 157* - Relazione al Ministero della Sanità, 1967.

* * * * *

Bibenzonium bromide

trimethyl-(1,2-diphenylethoxyethyl)ammonium bromide (MW 364.34)

Bibenzonium bromide is a synthetic drug with central sedative action, which acts as a cough sedative. It has none of the side effects present in the opiates.

Isoaminile

α -(isopropyl)- α -(β -dimethylaminopropyl)phenylacetonitrile citrate
(MW 244.37)

Isoaminile is a cough suppressant with no analgesic or respiratory depressant effects.

Oxeladine

α - α -diethyl-phenylacetic acid diethylamino-ethoxyethyl ester citrate

Oxeladine has a depressant action on cough reflexes at the peripheral level.

Benproperine

1-(2-benzyl-phenoxy)-2-(*N*-piperidino)-1-propane phosphate (MW 309.43)

Sodium dubunate

sodium 2,6-*d*-ter-butylmaphthalene sulphonate (MW 342.26)

Naphthoclizine

(1-(*p*-chlorobenzhydryl)-4-methylpiperazine)-di-ter-butyl-naphthalene sulphate

Pridinol

guaiaicol sulphonate of 1,1-diphenyl-2-piperidino-1-propanol (MW 295.41)

We have been unable to find any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. Although no harmful effects have been reported, we advise against their use in pregnancy, and in women of childbearing age who are likely to conceive.

Part 6

Hormones and antihormones

	Page
1. Steroid hormones	72
2. Hypophysial hormones	136
3. Thyroid and antithyroid drugs	152
4. Insulin, glucagon, and oral antidiabetic drugs	165

1. STEROID HORMONES

Some endocrine glands (adrenals) as well as the ovaries, testes, and placenta, produce steroid hormones with cholesterol as the starting material. The action of the steroid hormones presupposes the existence of specific protein receptors as target cells. In addition to the natural products, numerous synthetic drugs have been prepared. The following hormones are distinguished on the basis of their biological activity: corticosteroids, androgens and anabolic substances, oestrogens, progestins.

1.1 Corticosteroids

The adrenal cortex produces two classes of steroids, the mineralocorticoids and the glucocorticoids. The first group regulates the content of sodium and potassium in the organism, while hormones of the second group have a complex action on protein, carbohydrate, and lipid metabolism, on immunological responses, and on the appearance of inflammatory reactions. In synthetic drugs, anti-inflammatory and immunosuppressive actions have been significantly potentiated in relation to metabolic effects. The following are described in this section:

	Recommendation	Page
<i>Mineralocorticoids</i>		
Aldosterone	P	73
Desoxycorticosterone acetate	P	74
<i>Glucocorticoids</i>		
Cortisone acetate	P	74
Hydrocortisone	P	79
Hydrocortisone sodium succinate		79
Prednisone	P	80
Prednisolone	P	81
Prednisolone acetate	P	81
Prednisolone steaglate	P	81
Prednisolone succinate	P	81
Methylprednisolone	P	81
Methylprednisolone acetate	P	81
Methylprednisolone sodium succinate	P	81
Prednilidene	P	82
Beclomethasone	P	83
Dexamethasone	P	84
Triamcinolone	P	85
Betamethasone	P	85
Betamethasone sodium phosphate	P	86
Pregnenolone	P	87

During pregnancy, the use of the mineralocorticoids is limited to substitution therapy in Addison's disease, which is a matter of absolute necessity.

The glucocorticoids have to be used with care, even although some of their synthetic derivatives have not been reported as having teratogenic effects when administered in the first trimester. It is, however, necessary to note that they have a depressant effect on foetal adrenal cortex. The glucocorticoids stimulate the production of surfactant in foetal lungs, and are used in the prevention of the neonatal respiratory syndrome.

We do not think that there is sufficient information available to form an opinion on the use of the following in pregnancy: meprednisone, paramethasone acetate, fluprednisolone (page 88).

Metyrapone (page 88) is an inhibitor of the enzyme 11- β -hydroxylase which blocks the biosynthesis of cortisol and aldosterone. It is used exclusively as a diagnostic aid, and should be administered with care in pregnancy.

1.1.1. Mineralocorticoids

Aldosterone

Aldocorten, 11- β -21-dihydroxy-3,20-dioxopregnen-18-al (MW 360.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Aldosterone is the most potent mineralocorticoid produced by the adrenal cortex, and is synthesized from progesterone by the formation of DOCA (desoxycorticosterone), and then corticosterone. Aldosterone does not have an anti-inflammatory action, but it regulates sodium-potassium equilibrium, increasing renal excretion of potassium and of hydrogen, and reducing, at least initially, excretion of sodium. The detailed mechanism of action of the distal tubular cells is still under investigation. Aldosterone has been used in association with glucocorticoids in substitution therapy in Addison's disease.

Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, aldosterone should be used with care in pregnancy because of possible electrolyte imbalance.

No experimental studies have been described on the use of aldosterone in pregnancy in laboratory animals.

Desoxycorticosterone acetate or desoxycortone or DOCA

21-acetoxypregnene-3, 20-dione (MW 372.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Desoxycorticosterone is a mineralocorticoid, a precursor of corticosterone and of aldosterone, and it stimulates the retention of sodium and the excretion of potassium without having the other effects of the glucocorticoids (see cortisone, page 75). As opposed to the other adrenal steroids, desoxycorticosterone is almost completely destroyed in the digestive tract, and is therefore practically inactive orally. It is about 30 times less potent than aldosterone, and is used in the therapy of Addison's disease and in other situations where there is adrenal cortex insufficiency.

Desoxycorticosterone should be administered with care in pregnancy, especially in the first trimester, when there may be signs, although rare, of masculinization of the female foetus following its use [1]. Other authors, however, have never reported any malformations in the neonates when using doses of 20–40 mg/day at various stages of pregnancy [7].

In the mouse and rat, desoxycorticosterone was not teratogenic [2, 3, 4]. In the rat, at doses of 1 mg/day from the 4th day to the end of pregnancy, it caused neonatal hypertension which continued for as long as 1 year after birth [2]. In the mouse, doses of 0.1–1.25 mg from the 11th to the 14th day of pregnancy were not teratogenic [3], and subcutaneous doses of 1–2 mg/day for 4–6 days after mating did not affect the course of the pregnancy [4]. The distribution of ^{14}C -desoxycorticosterone was studied in the mouse foetus, and radioactivity in the palate was no higher than in any other tissue [5].

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1.1.2 Glucocorticoids***Cortisone acetate***21-acetoxy-17 α -hydroxypregnene-3, 11, 20-trione (MW 402.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Cortisone is a glucocorticoid produced in the adrenal cortex from progesterone, by formation of hydroxy-progesterone and cortisol (hydroxycortisone). This biosynthesis is controlled by ACTH (see page 139) and occurs continuously, as there is no storage capacity for preformed hormones. The corticosteroids, particularly cortisol, control protein synthesis by regulation transcription of the genetic information contained in RNA, stimulation glucogenesis from proteins and from pyruvate, and glycogen synthesis. These hormones also reduce peripheral utilization of glucose and facilitate lipolysis by catecholamines.

The corticosteroids reduce blood viscosity and capillary permeability and tend to increase plasma volume and arterial pressure, the half life of haemoglobin, and the percentage of neutrophils. They depress eosinophils, basophils, lymphocytes, and monocytes. They act on the central nervous system, elevating mood and excitability. Cortisone derivatives diminish the mass of lymphatic tissue, delayed (cellular) immunological responses, hypertensive reactions, and inflammation.

Administration of corticosteroids in pharmacological doses to growing individuals neither retards nor blocks body development. DNA synthesis is inhibited (DNA polymerase) and thus cellular duplication in many tissues (connective tissue, liver, brain, mucosa, thymus).

Cortisone and its derivatives are used in substitution therapy for adrenal cortical insufficiency, and for the treatment of some blood diseases (autoimmune haemolytic anaemia, thrombocytopoenic puerpura, leukaemia, etc.), but in particular as anti-inflammatories, antireactives, and immunosuppressants, both locally and systemically.

All the corticosteroids, with the exception of DOCA (desoxycorticosterone acetate), are rapidly absorbed in the digestive tract, and more slowly by the intramuscular route. They are bound to plasma proteins (globulins, and also albumin), dissolve in all tissues and organic liquids, are metabolized in the liver, and excreted in the urine in the form of 17-hydroxycorticosteroids. The synthetic derivatives are more potent than the naturally occurring steroids because of their lower affinity for plasma proteins and their slower metabolism.

Systemic administration of corticosteroids is contra-indicated in patients with peptic ulcer, osteoporosis, psychoses, diabetes, infectious illnesses, and congestive heart failure. In addition, they may depress adrenal secretion and modify responses to anticoagulant drugs by increasing the coagulability of blood.

Cortisone acetate, being a glucocorticoid, causes sodium retention, and therefore it has been replaced by synthetic drugs which are less likely to cause this problem.

Like all steroids, cortisone crosses the placental barrier, because of its lipid solubility, but not to any great extent. Administration of cortisone in pregnancy should be carried out with caution, because there are many reports of abortion and teratogenic effects (particularly cleft palate) related to its use [1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 28, 29, 31, 34, 60, 63, 67, 70, 74, 79]. Five cases of foetal malformations have been reported (cataract, hypospadias, coarctation of the aorta, etc.) in 30 infants of mothers who had taken cortisone in the first trimester at a dose of 50 mg/day [7]. In a retrospective study on 260 patients who had taken the drug in pregnancy, eight produced dead fetuses, and seven gave birth to infants with malformations [10].

Two infants, affected respectively with gastroschisis and hydrocephalus, were born to mothers treated with cortisone before and throughout pregnancy [11]. A case of anencephaly has been described in an infant born to a mother who had taken the drug in pregnancy. An infant with Fallot's tetralogy was born to a mother who was given cortisone therapy during pregnancy [14]. Asphyxia and cleft palate were noted in the offspring of a mother who had taken cortisone in the first trimester [8]. Among 15 women who had taken cortisone for rheumatic ailments, there was one case of cleft palate in the offspring [19]. In 111 women who had taken cortisone in the first trimester, there were five cases of abortion, nine of foetal malformation, one neonate with acute adrenal insufficiency, one dead foetus, and one which died within a few days of birth [21].

Other authors maintain that cortisone has no adverse effects and is therefore not contraindicated in pregnancy [2, 9, 30, 32, 33, 35, 36, 37, 61, 62, 68, 72, 75, 78]. Some also believe that cortisone should be used with care during the last trimester because of possible inhibition of the foetal adrenal cortex [22, 23, 24, 25, 26, 27, 65, 73]. In 33 pregnant women treated with cortisone at a dose of 3–4 mg/day in the first trimester, there were no malformations [30]. Two patients were treated with cortisone throughout pregnancy, with no side effects in the foetus or the mother [33].

More recently, therapy with corticosteroids has been proposed in pregnant women with threatened premature abortion, in order to accelerate maturation of the foetal lungs and to prevent the development of neonatal respiratory syndrome [38, 39, 40, 69, 76]. The mechanism of action of the glucocorticoids in this respect is uncertain. According to some authors, they stimulate the secretion of surfactant by the pneumocytes [39], and according to others, they act as enzyme inducers in the synthesis of tensio-active lecithin [41].

Cortisone passes into breast milk [77].

In the mouse, rabbit, and chick embryo, cortisone had both embryotoxic and teratogenic effects [16, 17, 28, 42, 43, 44, 46, 53, 54, 55, 64]. In the rat, cortisone had embryotoxic effects, but rarely gave rise to cleft palate [9, 47, 48,

49, 50, 51, 52, 57, 58, 59, 66]. Doses of 20 mg/kg from the 9th to the 20th day of pregnancy were neither embryofoetotoxic nor teratogenic [48]. A subcutaneous dose of 0.5 mg/kg from the 11th to the 16th or from the 16th to the 19th day of pregnancy was not embryotoxic [49]. An intramuscular dose of 10 mg/kg from the 8th to the 20th day caused skeletal malformations in the neonates [50]. Early eruption of the incisors was noted in rats from mothers which had received cortisone from the 15th to the 20th day of pregnancy [51]. Administration of cortisone to the mothers in the last period of gestation caused a reduction in the weight of the foetal adrenals [52]. A dose of 20 mg/day caused growth retardation in the foetuses, and an increase in perinatal mortality, as well as a retardation in development of the survivors [58]. Administered at various stages of pregnancy, the drug caused the birth of low weight foetuses, but it was not teratogenic [66].

In the mouse, intramuscular doses of 2.5 mg/day at various stages of gestation caused cleft palate [42]. Subcutaneous doses of 2.5 mg/kg from the 11th to the 15th day of pregnancy caused cleft palate [43]. An intraperitoneal dose of 0.25 mg/kg from the 12th to the 14th day caused 100% foetal resorption [44].

In the rabbit, subcutaneous doses of 25–40 mg/kg caused cleft palate in 50% of foetuses [53]. At a dose of 25 mg/kg from the 10th to the 23rd day, cortisone was embryofoetotoxic [54]. A subcutaneous dose of 15 mg was embryotoxic, and also appeared to extend the period of gestation [55].

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Hydrocortisone or cortisol

Daktacort, Efcortelan, Hydrocortistab,

11 β , 17 α , 21-trihydroxy-pregnene-3, 20-dione (MW 362.5)

Hydrocortisone sodium succinate

Solu-Cortef (MW 484.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Hydrocortisone is a derivative of 17-hydroxyprogesterone, is the precursor of cortisone, and is the glucocorticoid hormone secreted by the adrenal glands. It increases glomerular filtration, and is mainly metabolized outside the liver. For further information, see cortisone (page 74). Hydrocortisone sodium succinate is used intravenously or intramuscularly in emergency therapy.

The use of hydrocortisone during pregnancy has the same limitations as those of cortisone (see page 74), and hydrocortisone has the same applications in the prevention of neonatal respiratory syndrome [14, 15].

In the mouse, rat, rabbit, and hamster, hydrocortisone was teratogenic [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. In the rat, subcutaneous doses of various amounts, given from the 14th to the 21st day of pregnancy, were embryofoetotoxic, causing an increase in foetal resorptions [1]. In the mouse, a dose of 2.5 mg on the 10th or 11th day of pregnancy was teratogenic, causing cleft palate [4]. A parenteral dose of 4 mg, from the 11th to the 18th day of pregnancy, caused cleft palate in 18% of neonates [5].

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Prednisone

Decortisyl, Deltacortone,

17 α -21-dihydropregnadiene-3,11,20-trione (MW 358.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Prednisone is a synthetic glucocorticoid, with an anti-inflammatory action five times greater than that of cortisone and with a smaller tendency to cause sodium and water retention. It is therefore used as a diuretic in nephrotic oedema. It is transformed into prednisolone in the organism (see page 82). Prednisone is also used as an immunosuppressant, and is often given in association with azathioprine, during and after organ transplants. For other information, see cortisone (page 74).

Several reports indicated that administration of prednisone is without harmful effects in pregnancy [2, 3, 4, 5, 6, 7, 14]. In pregnant women who had had a renal transplant, treatment with prednisone at doses of 15–45 mg/day in association with other immunosuppressants, caused no foetal or placental damage [2, 3]. No harmful effects were observed in the infants of patients with Wegener's granuloma, who were treated throughout pregnancy with prednisone at a dose of 15 mg/day and with azathioprine [6], as was also the case with the infant of another patient who remained pregnant during treatment with prednisone [4]. Prednisone administered to 40 pregnant women with bronchial asthma at various stages of pregnancy did not cause adrenal insufficiency in the foetus, but in one case neonatal jaundice was observed [14].

In a retrospective study on 34 patients treated with prednisone during pregnancy, a marked retardation in foetal growth was noted, as well as inhibition of placental development [15]. A single case of labioschisis was reported in the offspring of a patient treated for rheumatism with prednisone during the first trimester [10]. High doses of prednisone administered in the last trimester inhibited the foetal hypophysis and adrenals [11]. In the neonate of a patient treated in the last week of pregnancy with high doses of prednisone [40 mg/day] adrenal insufficiency occurred a few days after birth. This resolved with cortisone

and ACTH therapy [11]. The results of using prednisone in the treatment of gestosis have not proved satisfactory [12,13].

In the mouse and rat, prednisone was teratogenic [1].

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Prednisolone or delta-hydrocortisone

Codelcortone, Codelsol, Cordex, Delta-Cortef, Deltacortril,
11 β , 17 α , 21-trihydroxypregnadiene-3, 20-dione (MW 360.5)

Prednisolone acetate

Deltastab (MW 402.5)

Prednisolone steaglate

(MW 685.0)

Prednisolone succinate

(MW 460.5)

Methylprednisolone

Medro- Cordex, 11 β , 17 α , 21-trihydroxy-6 α -methylpregnadiene-3, 20-dione
(MW 374.5)

Methylprednisolone acetate

Depo-Medrone (MW 416.5)

Methylprednisolone sodium succinate

(MW 496.5)

Predinilidene

16-methylene-prednisolone (MW 372.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Prednisolone and its methylated derivatives are synthetic glucocorticoids five times more active than cortisone. The acetylated derivatives are slightly water soluble and are used for depot injections by the intramuscular and intra-articular routes, while the succinates are water soluble and are used intravenously. Prednisolone is a metabolite of prednisone. For further information, see cortisone (page 74).

The effects arising from the administration of prednisolone in pregnancy are controversial. While some authors maintain that therapy with the drug is without harmful effects even during the first trimester [1, 2, 7, 9, 10], others believe that it is contra-indicated because of possible embryofoetotoxic effects, such as increase in foetal resorption and perinatal mortality, and teratogenesis (cleft palate) [3, 4]. In ten patients treated with prednisolone from the first trimester there was one abortion and two intra-uterine deaths, although these were not thought to be related to the drug [1]. Nine patients treated during conception and the first trimester with prednisolone at a dose of 5–10 mg/day had healthy infants [2], and 21 patients with bronchial asthma treated with prednisolone at various stages of pregnancy had healthy offspring, with one exception, not believed to be due to the drug [8].

Other investigations showed that among 34 patients treated with prednisolone there were eight cases of intra-uterine death and nine foetuses at high risk, while in other high risk pregnancies not treated, there was only one case of intra-uterine death and three premature births [3]. In a study on 30 patients treated with prednisolone in pregnancy, there were eight cases of intra-uterine death, two of anencephaly, and three of premature birth [4].

Prednisolone passes into breast milk [7]. Administered at a dose of 5 mg during lactation, 0.1% passed into the milk, and there were no side effects in the infant [7].

In the rat and mouse, prednisolone was foetotoxic [5] and teratogenic [6]. In the rat, prednisolone administered orally at a dose of 5 mg from the 5th day to the end of pregnancy did not cause suppression of foetal adrenals, but provoked inhibition of placental growth with consequent placental insufficiency and foetal death [5]. In the mouse, doses of 0.5 mg/day in the first stage of gestation caused cleft palate in 77% of neonates [6].

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Beclomethasone dipropionate

Beconase, Propaderm,

9 α -chloro-16 β -methylprednisolone dipropionate (MW 521.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Beclomethasone is a synthetic corticosteroid for topical use, and has no significant systemic activity. It is used by inhalation and is partly deposited in the bronchial mucosa, where it is hydrolyzed. It passes into the circulation and binds to plasma proteins to the extent of 87%, and is then metabolized by the liver to polar metabolites which are inactive and are eliminated in the bile and urine. The material deposited in the pharynx is 90% absorbed.

Beclomethasone has been used in 20 patients during pregnancy without embryofoetotoxic or teratogenic effects [1]. Twenty out of 600 patients treated with beclomethasone who subsequently became pregnant had normal infants. There were no abortions [1]. It is, however, worth remembering that the effects of administration of methylprednisolone, of which beclomethasone is a derivative, are controversial (see cortisone, page 74), and that the manufacturers advise against its use in the first trimester [2].

In the rat, beclomethasone administered orally at a dose of 0.1–10 mg/kg or by inhalation at a dose of 0.1 mg/kg from the 1st to the 19th day of pregnancy had no embryofoetotoxic or teratogenic effects [2].

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DexamethasoneDecadron, 9 α -fluoro-16 α -methylprednisolone (MW 392.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Dexamethasone is a synthetic glucocorticoid with anti-inflammatory activity which is 30 times greater than that of cortisone, and is practically devoid of sodium retaining properties. For further information, see cortisone (page 74). Dexamethasone, in addition to the usual therapeutic indications for similar drugs, is also used diagnostically to test suppression of ACTH secretion, and thus of cortisol, since it is the most active of the natural or synthetic hormones in this respect.

Dexamethasone should be used with care in pregnancy, evaluating the therapeutic benefits to the mother against possible side effects in the foetus [1, 2, 3]. No teratogenic effects linked to the use of dexamethasone in pregnancy have been reported [4, 6].

Administration of dexamethasone at doses of 15–20 mg for long periods, even during the first trimester, did not cause foetal malformations [6]. The drug was administered to three patients at various times during pregnancy, including the first trimester, and one infant had cleft palate [9]. Administered orally at a dose of 2 mg three times daily for 4 days in 56 pregnant women beyond term, dexamethasone caused spontaneous labour in 35 cases, without harmful effects on the foetus [10]. Recently, dexamethasone has been used in the last stage of pregnancy, principally in the therapy of threatened premature birth, to reduce the incidence of neonatal respiratory syndrome [7, 8, 11]. Administration of 12 mg dexamethasone for 2 days prior to birth was sufficient to accomplish this [7]. An analysis of the results in a series of 118 premature births to mothers treated with dexamethasone for 1–7 days before delivery indicated that it was preferable to give the drug for at least 1 week [8].

In the rat, the sporadic appearance of cleft palate has been observed after administration of dexamethasone at various stages of pregnancy [5].

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Triamcinolone or fluoxyprednisolone

Kenalog, Leder cort, Lederspan,

9 α -fluoro-16 α -hydroxyprednisolone (MW 394.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Triamcinolone is a synthetic glucocorticoid, six times more active than cortisone as an anti-inflammatory, and virtually devoid of sodium retaining effects. For further information, see cortisone (page 74).

There are few references to the use of triamcinolone in pregnancy which suggest malformations related to its administration [1]. However, some authors [5, 6], basing their conclusions on very restricted numbers of cases, have reported side effects in the mother and the foetus as a result of treatment with triamcinolone in pregnancy. One patient treated for 2 years before and during pregnancy with 4–8 mg/day triamcinolone gave birth to a normal full-term infant [5]. No harmful effects were observed in the offspring of five patients treated with triamcinolone for bronchial asthma at various stages of pregnancy [6].

In the rat, mouse, and macaque mulatto, triamcinolone was teratogenic [1, 2, 3, 4]. In the mouse, a dose of 1 μ g/day from the 11th to the 14th day of pregnancy caused cleft palate [2]. In the macaque mulatto, a dose of 5–28 mg from the 37th to the 48th day of pregnancy was foetotoxic [3].

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Betamethasone

Betnelan (MW 392.5)

Betamethasone sodium phosphate

Betnesol,

9 α -fluoro-11 β , 17 α , 21-trihydroxy-16 β -methylpregnadiene-3, 20-dione
(MW 516.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Betamethasone is a glucocorticoid with an anti-inflammatory action about 35 times more intense than that of cortisone, and with a very minor sodium retaining action, equivalent to that of dexamethasone. It has similar indications and contra-indications to the other glucocorticoids (see cortisone, page 74).

Betamethasone crosses the placental barrier [7]. Administered in a dose of 6 mg/day for 3 days to 16 pregnant women in order to accelerate maturation of the foetal lungs, the drug crossed the placenta and appeared in the foetal circulation and amniotic fluid. During treatment, the concentration of the drug was the same in maternal blood, cord blood, and amniotic fluid [7].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3]. Betamethasone has been used, like other cortisone-like drugs, in the last stage of pregnancy to prevent the neonatal respiratory syndrome [1, 4, 5, 6, 8, 9, 11, 12, 13]. The drug was administered to 14 pregnant women (29th–36th week) in whom amniocentesis had demonstrated a lecithin/sphingomyelin ratio of less than 2.2. In the second amniocentesis this ratio had increased, and no neonate presented with respiratory syndrome [8]. A retrospective study on the foetal and neonatal effects of betamethasone administration in women with threatened premature birth in order to avoid hyaline membrane disease in the infant showed that administration of the drug could increase the risk of neonatal infection by interfering with the antibacterial function of the polymorphonuclear leucocytes [9].

In the rat and rabbit, betamethasone caused cleft palate [2] and diminished birth weight [14]. Administered to macaque mulatto monkeys at a dose of 3 mg 24 and 48 hours before parturition, betamethasone produced an increase in liver glycogen in the neonates, with more rapid differentiation in the brain, lungs, liver, and adrenals [10].

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Pregnenolone

3 β -hydroxypregnen-20-one (MW 316.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Pregnenolone is the precursor of all the adrenocortical steroids. It is converted into dehydroepiandrosterone, giving rise to the androgens (androstendione and testosterone). It is transformed into progesterone, and can thereby form the basis of the mineralocorticoids (desoxycorticosterone \rightarrow corticosterone \rightarrow aldosterone) and to the glucocorticoids (17 α -hydroxypregesterone \rightarrow corticosterone \rightarrow cortisone). This transformation also occurs in the foeto-placental system.

Pregnenolone is used as an anti-inflammatory in the treatment of rheumatoid arthritis, at doses of 500 mg/day either orally or parenterally. It is however, less active than cortisone (50–400 mg/day).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, but in view of the nature of this drug, it should be used with care in pregnancy (see cortisone, page 74). Pregnenolone has been used in labour by some workers [1] to regularize uterine contractility. Administered to 12 women in labour at a dose of 3 mg/kg given intravenously for a period of 45 minutes, the drug reduced the frequency of contractions but did not alter their intensity [1].

No experimental studies have been described on the use of pregnenolone in pregnancy in laboratory animals.

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* * * * *

Meprednisone

16 β -methylprednisone (MW 372.4)

Meprednisone is a synthetic glucocorticoid hormone, more active than prednisolone with regard to anti-inflammatory activity, but with no mineralocorticoid actions. For other information, see prednisone (page 82).

Paramethasone acetate

6 α -fluoro-16 α -methylprednisolone-21-acetate (MW 434.5)

Paramethasone is a synthetic glucocorticoid with no mineralocorticoid activity, and with anti-inflammatory activity 12 times greater than that of cortisone (see page 74).

Fluprednisolone

6 α -fluoro-prednisolone (MW 378.4);

Fluprednisolone is a synthetic glucocorticoid with an anti-inflammatory activity 12 times greater than that of cortisone and with fewer side effects. For further information, see cortisone (page 74).

We have been unable to find any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. Although no harmful effects have been reported, we recommend that these drugs should not be used in pregnancy, or in women of childbearing age who are likely to conceive.

Metirapone

2-methyl-1, 2-dipyridyl(3')-1-oxopropane (MW 226.27)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic		P	P		

To be used with care in pregnancy.

Metirapone blocks the production of cortisone and aldosterone by inhibition of the enzyme 11 β -hydroxylase. Metirapone has been used in the therapy

of hyperaldosteronism. It can cause side effects ascribable to absence of glucocorticoids, and since the introduction of drugs which are aldosterone antagonists, metyrapone has been abandoned in current therapy and is used only as a functional test of hypophyseal activity (production of ACTH).

No teratogenic effects have been described following the administration of metyrapone, but the drug should be used with care in pregnancy because of the poor metabolic capacity of the foetus and the neonate [1, 2, 3]. Experiments conducted in dead foetuses perfused with metyrapone and pregnesterone have demonstrated that 11β and 11α hydroxylation were inoperative, while 17α hydroxylation was only partial. Sulphate conjugation was normal [4]. Metyrapone was used to evaluate adrenocorticoid reserves in the foetus in 20 cases in the second and third trimesters of pregnancy. From an evaluation of urinary oestriol, it was found that the foetal hypophysis also responded to this test [5].

In laboratory animals, metyrapone crossed the placental barrier, and affected foetal adrenals [6]. In the rat, when the drug was administered 2–3 days before the end of pregnancy, it prolonged the latter by as much as 36 hours, during which the foetus continued to grow [7]. At a dose of 30 mg given subcutaneously after adrenalectomy, on the 18th day of pregnancy, there was hypertrophy of the foetal adrenals. Before that day development of the adrenals was not affected, while after that day the effect was increasingly pronounced [8]. Administered at a dose of 0.4–4 mg/kg orally, metyrapone caused secondary effects during the pregnancy which were related to adrenalcortical hyperplasia [9].

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1.2 Androgens and anabolizing drugs

The androgenic hormones promote the development of sexual characteristics in the male, and also have an anabolic action. In numerous synthetic products, the latter property is particularly increased. Some of these drugs have been used in the treatment of breast cancer. The following drugs are discussed in this section:

	Recommendation	Page
Testosterone	C	90
Methyltestosterone	C	92
Fluoximesterone	C	93
Metandriol	C	93
Oxymesterone	C	95
Nandrolone	C	96
Metandrostenolone	C	96
Clostebol	C	97
Oxabolone cipionate	C	98
Stanozolol	C	98
Andro-isoxazol	C	99
Androstanolone	C	99
Norclostebol	C	100
Quinbolone	C	101
Mebolazine	C	101
Formebolone	C	102
Prasterone	C	103
Drostanolone propionate	C	103
Testolactone	C	104
Metenolone	C	105

During pregnancy, all the androgens and anabolizing substances are contra-indicated (feminine pseudohermaphroditism), and are generally not necessary.

We do not have sufficient information available on the following drug for a reliable assessment of its effects in pregnancy: octostanol (page 105).

Testosterone

Mixogen, Primoteston, Testorel (MW 288.41)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

In the male, testosterone causes the appearance of secondary sexual characteristics. It favours growth and development of the external genitalia, the prostate, and the seminal vesicles. At puberty, it causes growth of the beard,

enlargement of the larynx, and thickening of the vocal cords. Testosterone stimulates protein synthesis. This anabolizing effect is associated with retention of nitrogen, potassium, and calcium, and is important in promoting muscular and skeletal development. Administration of the drug in women causes virilization, the degree and reversibility of which is related to the dose and the duration of treatment.

Like all androgens [3], testosterone crosses the placental barrier. Therapy with testosterone during any period of pregnancy is absolutely contraindicated because of its virilizing effects on the female foetus (feminine pseudohermaphroditism), which vary from a simple clitoromegaly to fusion of the outer lips, atrophy of Muller's ducts, and the formation of a pseudoscrotum [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 18, 21, 22, 23, 24, 28, 29, 33, 34, 35, 37, 38, 39, 40, 41, 42].

In the rat, mouse, rabbit, hamster, and chick embryo, testosterone at various stages of pregnancy caused virilization of the female foetus [11, 12, 13, 14, 15, 16, 20, 30, 32], hypophysial foetal lesions with effects on subsequent adult sex life because of a deficit in ovulation [7, 19, 25], and a high incidence of abortions and foetal resorptions [11, 26, 27].

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Methyltestosterone

Mixogen, Plex-Hormone, Potensan,

11 α -methyl-4-androsten-17 β -ol-3-one (MW 302.44)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Methyltestosterone is the first derivative of testosterone to be active orally, with a mechanism of action analogous to that of testosterone (anabolizing and androgenic).

Methyltestosterone crosses the placental barrier [6]. The use of this drug in pregnancy from the 3rd to the 20th week has caused cases of female pseudohermaphroditism, enlargement of the clitoris, fusion of the outer lips, and persistence of the urogenital vestibule [1, 2, 3, 4, 6, 8, 13, 14, 16, 17, 18, 23, 24, 25, 26, 28, 29, 30, 31, 32, 33, 34]. One case has been described of a woman who was treated from the beginning until the 6th month of pregnancy with doses totalling 6850 mg testosterone without virilization in the mother or the foetus [7]. Administration of 600 mg per month from the 7th week of pregnancy caused female pseudohermaphroditism [3]. The same effects were obtained by administration of 900 mg per month from the 11th week [10]. Oral administration to six pregnant women from the 2nd to the 6th month of pregnancy of 10 mg/day, and to eight pregnant women in the first month of pregnancy of 3 mg/day caused enlargement of the clitoris in female foetuses [33, 34]. Administered to

ten pregnant women with albuminuria at a dose of 100 mg/day for 9 days at the end of pregnancy, methyltestosterone caused an increase in proteinaemia and a slight but obvious reduction in oedema [15].

In laboratory animals, methyltestosterone possessed a masculinizing action on the female foetus [11, 19, 20, 21, 22].

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Fluoximesterone

9 α -fluoro-11 β -hydroxy-17 α -methyltestosterone (MW 336.45)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Fluoximesterone is a synthetic androgen, active orally, and more potent than methyltestosterone. It has an intense anabolizing action besides having virilizing effects. Alkylation in position 17 makes it impossible for the drug to be aromatized in the placenta, and thus to be transformed to an oestrogen.

The use of fluoximesterone in pregnancy is contra-indicated [1, 2, 3, 4, 5, 6, 7] because of possible effects on the foetus.

No experimental studies have been described on the use of fluoximesterone in pregnancy in laboratory animals.

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Metandriol

17 α -metylandrost-5-ene-3 β , 17 β -diol (MW 304.46)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Metandriol is a synthetic anabolizing steroid with androgenic activity equivalent to about half that of methyltestosterone. As regards the anabolic action, opinions vary, but one view is that metandriol has a strong anabolic action with some androgenic activity, while others believe that the drug has no greater anabolic/androgenic ratio than testosterone or its esters [6].

Metandriol is contra-indicated in pregnancy because of its possible virilizing effects on female fetuses [1, 2, 3, 8, 9, 10, 11, 12, 13, 14, 15, 16]. Administration of 3200 mg metandriol intramuscularly to a patient in the third trimester caused clitoral enlargement without labial-scrotal fusion in the female foetus [8]. Administered intramuscularly at a dose of 2700 mg to a pregnant woman with breast cancer, the drug caused genital hypoplasia in the male foetus [14]. Administration of 50 mg/week sublingually to seven patients from the 2nd to the 8th month of pregnancy caused clitoral enlargement in female fetuses [15]. Administered sublingually to nine patients at a dose of 25 mg/day from the 3rd

to the 4th month of pregnancy, metandriol caused clitoral enlargement in female foetuses [16].

In the chick embryo, metandriol caused bone malformations [4].

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Oxymesterone

4-hydroxy-17 α -methyltestosterone (MW 318.44)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Oxymesterone is a derivative of methyltestosterone with low androgenic potency. It has a mainly anabolic action, which stimulates protein synthesis.

Oxymesterone is contra-indicated in pregnancy because of its virilizing effects on female foetuses [1, 2, 3, 4].

No experimental studies have been found on the use of oxymesterone in pregnancy in laboratory animals.

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Nandrolone

Durabolin, nor-androstenolone phenylpropionate (MW 274.39)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Nandrolone is a steroid derived from androstane, and has an anabolizing action (retention of nitrogen and increase in protein synthesis). Its androgenic activity is equal to 1/17th that of testosterone, and it also has a luteinizing action equal to ten times that of progesterone, but it cannot maintain pregnancy.

Nandrolone is contra-indicated in pregnancy because of its possible virilizing effects on the female foetus [1, 2, 3, 4, 6, 7].

In the rat, nandrolone was embryofetotoxic at high doses [8]. In the mouse, the phenomenon of 'enhancement' was observed in embryopathies arising from alloxan diabetes [5]. In the rat, nandrolone administered intramuscularly at a dose of 3.25 mg/kg from the 3rd to the 17th day of gestation caused no harmful effects on the mother, the pregnancy, or embryofoetal development. A dose of 65 mg/kg from the 3rd to the 17th day was embryofetotoxic [8].

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Metandrostenolone or metandienone

Dianabol, 17 α -methyl-17 β -hydroxy-androsta-1,4-dien-3-one (MW 300.42)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Metandrostenolone is a synthetic steroid derived from testosterone, and is a relatively weak androgen with pronounced anabolic effects.

Metandrostenolone is contra-indicated in pregnancy because of its possible virilizing effect on female fetuses [1, 2, 3, 4, 5, 6, 7]. The manufacturers concur with this view [8].

No experimental studies have been found on the use of metandrostenolone in pregnancy in laboratory animals.

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Clostebol

4-chlorotestosterone acetate (MW 322.89)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Clostebol is a synthetic steroid derived from testosterone and used principally for its anabolic effect. It does, however, have a virilizing action equal to about 1/5th that of testosterone. Clostebol has been widely tested both in animals and in man, and possesses a certain antiseptic activity in addition to its strong anabolizing properties. It encourages the healing of fractures, surgical wounds, and torpid sores. In paediatrics it has proved invaluable in the treatment of children and those with dystrophia.

Clostebol is contra-indicated in pregnancy because of possible virilizing effects on the female fetus [1, 2, 3, 4, 5, 6, 7, 8].

No experimental studies have been found on the use of clostebol in pregnancy in laboratory animals.

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Oxabolone cipionate

4-hydroxy-19-nortestosterone 17-cyclopentylpropionate (MW 414.59)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Oxabolone is a derivative of nortestosterone with anabolic activity superior to that of nortestosterone and androgenic action equal to 1/17th that of testosterone. Oxabolone stimulates protein synthesis and favours nitrogen retention. Like all 19-nor derivatives, it also possesses a luteinizing action equal to ten times that of progesterone, but this is insufficient to maintain pregnancy.

Oxabolone is contra-indicated in pregnancy because of its possible virilizing effects on the female foetus [1, 2, 3, 4, 5, 6, 7, 8].

No experimental studies have been found on the use of oxabolone in pregnancy in laboratory animals.

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Stanozolol

17 β -hydroxy-17 α -methylandrostan-(3,2-c)pyrazol (MW 328.48)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Stanozolol is an anabolizing steroid with a weak androgenic action, and it is active orally.

Stanozolol is contra-indicated in pregnancy because of possible virilizing effects on the female foetus [1, 2, 3, 4, 5, 6, 7, 8].

No experimental studies have been found on the use of stanozolol in pregnancy in laboratory animals.

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Andro-isoxazol

17 β -hydroxy-17 α -methyl-androstan(3, 2-*c*)isoxazole (MW 329.47)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Andro-isoxazol is a synthetic androgen with a mainly anabolizing action, and slight androgenic effects.

The use of andro-isoxazol in pregnancy is contra-indicated in pregnancy because of possible virilizing effects on the female foetus [1, 2, 3, 4].

No experimental studies have been found on the use of andro-isoxazol in pregnancy in laboratory animals.

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Androstanolone or dihydrotestosterone or stanolone

androstan-17 β -ol-3-one (MW 290.43)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Androstanolone is a synthetic derivative of testosterone with an androgenic action equal to that of methyltestosterone. It is administered sublingually and also has a strong anabolizing action, sufficient to increase the ratio of anabolizing activity to androgenic activity to 4:1 [4].

Androstanolone is contra-indicated in pregnancy because of possible virilizing effects on the female foetus [1, 2, 3, 5, 6].

No experimental studies have been described on the use of androstanolone in pregnancy in laboratory animals.

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Norclostebol

4-chloro-19-nortestosterone acetate (MW 308.67)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Norclostebol is a synthetic steroid derivative of testosterone, used principally as an anabolizing drug. It possesses an androgenic action equal to 1/17th that of testosterone, and also has a luteinizing action equal to ten times that of progesterone. It cannot, however, support pregnancy.

Norclostebol is contra-indicated in pregnancy because of possible virilizing effects on the female foetus [1, 2, 3, 4, 5, 6, 7, 8].

No experimental studies have been found on the use of norclostebol in pregnancy in laboratory animals.

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Quinbolone

17-cyclopentenyl ether of δ 1,4-androstandienolone (MW 352.52)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Quinbolone is a steroid of the androstane series, with a protein anabolizing action and a weak virilizing effect.

Quinbolone is contra-indicated in pregnancy because of its possible virilizing effects on the female foetus [1,2,3,4].

No experimental studies have been found on the use of quinbolone in pregnancy in laboratory animals.

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Mebolazine or dimetazine

2 α -17 α -dimethyl-5 α -androstan-17 β -ol-3,3'-azine (MW 632.6)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Mebolazine is a derivative of androstane with a notable anabolic action. It is also myotrophic, completely free of toxicity, and has very limited androgenic

activity. It is used in the therapy of osteoporosis because it aids healing of fractures and can correct protein deficiency.

Melbolazine is contra-indicated in pregnancy because of possible virilizing effects on the female foetus [1, 2, 3, 4, 5, 6, 7, 8].

No experimental studies have been found on the use of melbolazine in pregnancy in laboratory animals.

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Formebolone

2-formyl-11 β , 17 α -dihydroxy-17 α -methyl-androsta-1, 4-diene-3-one
(MW 652.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Formebolone is an anabolizing steroid derived from androstane and is water soluble.

Formebolone is contra-indicated in pregnancy both because of reported clinical experience and because of its resemblance to other anabolizing steroids [1, 2, 3, 4].

In the rat and rabbit, formebolone had no virilizing effects on the foetus' [5]. In the rat, doses of 0.5–1 mg/kg for 12 days from mating, and in the rabbit, similar doses for 14 days from mating, were neither foetotoxic nor teratogenic [5].

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Prasterone or dehydro-epiandrosterone or dehydro-isoandrosterone sulphate
 3 β -hydroxy-androsten-17-one (MW 288.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Prasterone is a natural hormone, weakly androgenic, which is used in the therapy of psychic hypo-evolutism and in oppressive states, as well as in andropause and the menopause.

Although there are no reports of harmful effects on the human foetus, the mother, or the pregnancy, prasterone is contra-indicated in pregnancy because of possible virilizing effects on the female foetus.

In the rat, prasterone administered at a dose of 100–280 mg at various stages of pregnancy caused virilization of the female foetus [1]. However, other authors [1,2] deny the existence of any virilizing effects on the female, or feminizing effects on the male foetus in the rat [3,4]. Another study showed that subcutaneous doses of 1–25 mg/kg from the 12th to the 20th day of pregnancy did not cause any virilizing or feminizing effects [3]. Similar results have been reported by other authors [4].

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Drostanolone propionate

2 α -methyl-17 β -hydroxy-androstan-3-one propionate (MW 360.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Drostanolone is a synthetic steroid derivative of androstane. It is used particularly as an inhibitor of mammary tumour growth, and to prevent metastases.

Drostanolone is contra-indicated in pregnancy because of its androgenic activity, even although this is less than that of other similar drugs [1]. Other authors concur with this view [2, 3].

No experimental studies have been found on the use of drostanolone in pregnancy in laboratory animals.

For further information, see testosterone (page 90).

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Testolactone

17 α -oxo-D-homo-1,4-androstadiene-3,17-dione (MW 300.38)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Testolactone is a synthetic steroid with antineoplastic activity. Its mechanism of action is not clear, but it is presumed to have an indirect influence on DNA synthesis, thus interfering with proliferation of tumour cells. A variation in the RNA/DNA ratio has been demonstrated following the use of testolactone, with an increase in RNA, and a parallel decrease in DNA. Testolactone has no androgenic activity in humans or animals.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, but the use of testolactone is not advised in pregnancy, since little is known about its effects on the foetus [1, 2].

No experimental studies have been described on the use of testolactone in pregnancy in laboratory animals.

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Metenolone

1-methyl- δ -1-androsten-17 β -ol-3-one-17 β oenanthate (MW 302.44)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Metenolone is an anabolizing steroid which also possesses a weak virilizing action. It stimulates body growth and cellular multiplication. The absence of alkyl groups in position 17 renders it free from hepatotoxicity. Metenolone has only slight influence on the adrenal glands and the hypophysis, and is not aromatized to oestrogen in the placenta. It therefore acts as the parent compound on the foetus [1].

Metenolone is contra-indicated in pregnancy because of virilizing effects in the female foetus [2, 3, 4, 6, 7, 8, 9].

In the rabbit, rat, and mouse, metenolone caused abortions when administered in the early stages of pregnancy [5].

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* * * * *

Octostanol

dihydrotestosterone 3-*n*-octyl enol ether (MW 402.6)

Octostanol is an analogue of testosterone and is used intramuscularly in the therapy of malignant mammary tumours. Its anabolizing action is greater than its androgenic activity.

We have been unable to find any information about the effects of this drug in pregnancy, either in the literature or from the manufacturer. In view of this lack of information, we advise against its administration in pregnancy, and in women of childbearing age who are likely to conceive.

1.3 Oestrogens

The oestrogens promote the development of female sexual characteristics and at the same time play an important metabolic role. The production of oestrogens is increased during pregnancy, when they assume a particular significance in the reproductive process. In addition to the naturally occurring oestrogens, there are numerous synthetic or non-steroid substances available. In fact, oestrogenic activity is connected with a low structural specificity. The following drugs are discussed in this section:

	Recommendation	Page
Oestradiol	P	106
Oestradiol valerianate	P	106
Oestradoil benzoate	P	108
Quinoestradiol	NC	110
Oestrone	P	110
Oestriol	NC	111
Oestrogens, conjugated	P	112
Ethinylestradiol	P	112
Diethylstilboestrol	C	113
Hexoestrol	C	116
Dienoestrol	C	116
Zeranol	P	117
Phosphestrol	C	118
Tamoxifen	C	118

Oestrogen therapy in pregnancy has a substitutive significance, particularly in the first trimester. Conjugated oestrogens and their derivatives, with the exception of oestriol, should be used with care, because of possible virilization of the female foetus. On the other hand, the stilbenes are contra-indicated because of the possible induction of vaginal adenocarcinoma in the female offspring of women thus treated in pregnancy.

We maintain that there is insufficient information on the following drugs to be able to provide an informed opinion on their use in pregnancy: chlorotrianisene, metallenioestriol, quinoestrol (page 119).

Oestradiol

oestra-1, 3, 5-(10)-triene-3,17 β -diol (MW 272.4)

Oestradiol valerianate

Progynova,

17 β -valerianyloxyoestra-1, 3, 5(10)-triene-3-ol (MW 356.5)

Oestradiol benzoate

3-benzoyloxy-oestra-1, 3, 5(10)-trien-17 β -ol (MW 376.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P	P	P		

To be used with care in pregnancy.

Oestradiol is the most potent natural oestrogen, produced mainly by the ovaries (theca interna) as a result of the action of the hypophysial gonadotrophic hormones. The luteinizing hormone (LH) links to a receptor which is present in the membrane of the target cell and gives rise to the synthesis of prostaglandins, which activate the enzyme adenylycyclase. In the cell, ATP (adenosine triphosphate) is then transformed into cyclic AMP (adenosine monophosphate) which metabolizes cholesterol, produced from acetate in the ovary, into pregnenolone, the precursor of all the steroid hormones. Androstenedione, which is formed from dehydroepiandrosterone or from progesterone, is the direct precursor of testosterone and of the oestrogens. In the ovary, the androgens (testosterone and androstenedione) are demethylated and aromatized, giving rise respectively to oestradiol and oestrone. The principal product is always oestradiol, which is oxidized in the liver to oestrone. The latter is hydrated to a less active product, oestriol.

Oestriol, therefore, is not produced in the ovary, but is simply a peripheral metabolite. Metabolism of androstenedione and of testosterone, and thus the formation of the oestrogens described here, not only occurs in the ovary but also in other tissues, for example adipose tissue.

During pregnancy, synthesis of oestrogens occurs mainly in the foeto-placental unit, starting from foetal adrenal dehydroepiandrosterone, which may be metabolized by the foetal liver and the trophoblast to oestriol. To a lesser degree, epiandrosterone is directly transformed into oestrone and oestradiol by the placenta, through an androgenic step (androstenedione—testosterone) analogous to that in the ovary.

The oestrogens act only on target cells in the female genital tract, in the breast, in the hypothalamus and the hypophysis, which have specific receptors. The steroids which are transported by a protein pass into the cytoplasm and then into the nucleus, where they modify the synthesis of RNA, proteins, and DNA. This causes a series of modifications in the target organs, which have been well documented clinically. They include proliferation of the Müllerian tissue, the breast, the cutaneous structures connected with secondary sexual characteristics, and with cartilage connected with the long bones (at higher doses, on the other hand, there is inhibition of growth). The oestrogens cause important metabolic changes, detailed below.

PROTEIN METABOLISM. This includes a slight anabolizing action (much weaker than that of the androgens), which is translated into retention of nitrogen. The increase in protein synthesis affects Müllerian contractile proteins as well as the cortisol protein carrier (transcortin), thyroxine (TBG, thyroxine-binding globulin), and hypertensinogenin (alpha-2 circulating globulin produced by the liver). This becomes translated into interference with the action of the glucocorticoids and of the thyroid, as well as with the possible appearance of hypertension.

GLYCOSIDE METABOLISM. The oestrogens reduce tolerance to glycosides, potentiating the effects of the glucocorticoids and reducing hepatic metabolism, modifying intestinal absorption of glucose, causing insulinaemia and altering plasma levels of growth hormone.

LIPID METABOLISM. The oestrogens increase plasma lipids, particularly the triglycerides and the phospholipids, potentiating lipogenesis and antagonizing the plasma-clarifying effect of heparin, mediated by lipoprotein lipase (see heparin, Vol. 1).

SALT-WATER BALANCE. The oestrogens cause retention of sodium and of water, leading to oedema. They also modify contractile responses of the myometrium by various feedback mechanisms through the hypothalamus and the hypophysis.

Oestradiol and the other natural oestrogens are rapidly absorbed through the skin, the mucosa, and in the digestive tract. They are partly transported by plasma proteins, and are inactivated in the liver and partly secreted in the bile, where enterohepatic recycling leads to simultaneous inactivation. This takes place via the oxidation of oestradiol to oestrone and successive hydration of the latter to oestriol, which is less active. Sulphate and glucuronide conjugation also take place. These polar derivatives enter cells with difficulty, and are eliminated in the urine.

Among the side effects caused by the oestrogens are nausea and vomiting (as in hyperemesis), anorexia, cephalaea, increase in photosensitivity, an increased incidence of thromboembolism, increase in otosclerosis, and functional overloading of the liver (cholestatic jaundice, a slight increase in retention of bromosulphthalein). It has, however, been clinically demonstrated that oestradiol, as opposed to mestranol, interferes less with hepatic function.

Therapeutic applications of the oestrogens are numerous. The naturally occurring oestrogens, such as oestradiol, have the same effects as the synthetic ones, and are generally less active orally. Oestrogen therapy should be carefully controlled in diabetic patients, in epileptics, in hypertensive patients, and in those with porphyria, tetanus, and multiple sclerosis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. Referring to data regarding the use of oestrogens in general in pregnancy, some authors, basing their opinions on their own clinical experience in the use of oestrogens in treatment of threatened abortion, believe that they are without harmful effects [1, 2, 3, 4, 5, 11, 12, 14, 15, 18, 20, 22, 23, 36]. Other authors, in consideration of sporadic references in the literature to malformations (virilization of the female foetus) with high doses of oestrogens believe that they should be used with care in pregnancy [6, 7, 8, 9, 10, 13, 16, 17, 19, 21].

In the mouse and rabbit, oestradiol caused abortions and was teratogenic [14]. In the mouse and rat, it was foetotoxic and teratogenic, causing an increase

in perinatal mortality [24, 25, 27, 28]. In the macaque mulatto, oestradiol was neither embryofetotoxic nor teratogenic [26]. In the sheep, oestradiol caused an increase in blood flow in the placenta [37]. In the rat, oestradiol at doses of 0.8–35 mg from the 13th to the 20th day of pregnancy caused feminization in the male (undescended testes, absence of epididymis, seminal vesicles and prostate, presence of a rudimentary vagina) and malformations of the genital tract in the female foetus [27, 28]. Administered on the 19th day of pregnancy, it caused hypertrophy of the adrenals in the female foetus, while from the 15th to the 16th day of pregnancy it caused hypospadias in the male. This effect has been explained by the inhibition of testicular testosterone and adrenocortico-steroid synthesis [29, 30]. Oestradiol also caused termination of pregnancy [31].

In the mouse, oestradiol at doses of 1 mg/day from the 11th to the 16th day of pregnancy caused cleft palate [34], while at doses of 5–7 mg on the 13th–14th day of pregnancy it affected development of the eyelids without affecting the eyes themselves [35].

In the macaque mulatto, doses of 4–25 mg/day in a single administration from the 28th to the 80th day of pregnancy had no embryofetotoxic or teratogenic effects [16].

In the sheep, oestradiol intravenously at doses of 1 mg/kg between the 38th and 139th day of pregnancy caused vasodilatation with increased blood flow in the myometrium, the endometrium, and the placenta. Cardiac output was increased by 14% [37].

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Quinoestradiol

Pentovis,

3-(cyclopentyloxy)oesra-1,3,5(10)-triene-16 α ,17 β -diol-oestriol-3-cyclopentyl ether (MW 356.5)

Not contra-indicated in pregnancy.

Quinoestradiol is derived from oestriol, and its action is principally on the inferior segments of the female reproductive system.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, at doses of 0.1–1 mmol by gastric intubation from the 6th to the 19th day of pregnancy, quinoestradiol possessed a feminizing action on the male foetus, and a virilizing effect on the female. It sometimes caused abortion [1].

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Oestrone or follicoline

Hormonin, 3-hydroxy-oesra-1,3,5(10)-trien-17-one (MW 270.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P	P	P		

To be used with care in pregnancy.

Oestrone is a natural oestrogen and is less potent than oestradiol. For further information, see oestradiol (page 106). Oestrone is administered orally or intramuscularly (oily solution or microcrystalline suspension in water).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3]. It is, however, worth referring to data in the literature concerning the use of oestrogens in general in pregnancy (see oestradiol, page 106).

In the mouse, oestrone administered halfway through pregnancy was embryotoxic and teratogenic [4, 5]. A dose of 1 mg/day from the 11th to the 16th day of pregnancy caused cleft palate in the foetus [5]. In the rat, doses of 0.05 mg/kg on the 9th day of pregnancy caused diminished aggressiveness in the offspring and a slowing of conditioned reflexes [6].

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Oestriol

Hormonin, Ovestin, oestra-1, 3, 5(10)-triene-3, 16 α , 17 β -triol (MW 288.4)

Not contra-indicated in pregnancy.

Oestriol is a natural oestrogen, a metabolite of oestradiol which is less active than the parent compound and oestrone. In pregnancy it is produced by the foeto-placental unit, and is used as a diagnostic test. It is active orally. For further information, see oestradiol (page 106).

Administration of oestriol by the intra-amniotic route at term, or after the end of a pregnancy, tends to increase uterine contractility and shorten the duration of labour [1].

Administration of oestriol is not contra-indicated in pregnancy.

In the rat, mouse, rabbit, and guinea-pig, oestriol and the other synthetic and natural oestrogens caused abortion [2, 3]. Some authors maintain that oestriol affects sexual differentiation of the foetus [5]. Administered to the rat at doses of 0.1–1 mmol by gastric intubation from the 16th to the 19th day of pregnancy, oestriol affected the mammary glands, caused feminization of the male foetus and virilization of the female, but did not cause resorption [5].

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Conjugated oestrogens

Premarin, prempak

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P	P	P		

To be used with care in pregnancy.

The preparation contains a mixture of conjugated oestrogens and is therefore water soluble. It is recovered from the urine of the pregnant mare. The principal active substances are oestrone sulphate (50–65%), and equine sulphate (20–35%). Conjugated oestrogens may be administered orally or intravenously, to control haemorrhage. The biological and pharmacological actions of this preparation resemble those of oestradiol (see 106).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy (see oestradiol, page 106). It is advisable, however, to consult the literature regarding the use of oestrogens in general in pregnancy (see oestradiol, page 106).

No experimental studies have been described on the use of conjugated oestrogens in pregnancy in laboratory animals.

Ethinylloestradiol

Anovlar, Eugynon, Minovlar, Ovulen, Microgynon, etc.,
17 α -ethinyl-oestra-1, 3, 5(10)-triene-3,17 β -diol (MW 296.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P	P	P		

To be used with care in pregnancy.

Ethinylloestradiol is a synthetic derivative of the natural hormone (see page 106) and is 20 times more active than the latter, even by the oral route. This is because of the slow inactivation of the drug in the liver and other tissues. During the course of therapy with ethinylloestradiol, as with other oestrogens, there is a greater risk of thromboembolism, particularly in the puerperium.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3,4], and our own experience supports this view. A study of 381 pregnant women with a history of repeated miscarriage was carried out. The women were treated with ethinyloestradiol at a dose of 1.5 mg/day for varying periods, from a few days to many months. No side effects were observed in the foetus [1]. It is, however, worth recalling data regarding the use of oestrogens in general in pregnancy (see oestradiol, page 106).

In the mouse, rat, and rabbit, ethinyloestradiol, like other natural and synthetic oestrogens, caused abortion [5].

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Diethylstilboestrol or stilboestrol

Tampovagin, 3, 4-di-*p*-hydroxyphenylhex-3-ene (MW 268.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C	C	C		

Contra-indicated in pregnancy.

Diethylstilboestrol is a synthetic non-steroid oestrogen, highly active orally and with slow metabolism. It is cheap to produce. Therapy with stilboestrol carries a greater risk of thromboembolism, particularly in the puerperium (increase in factor IX). For further information on the oestrogens, see oestradiol (page 106).

The use of stilboestrol in pregnancy has produced conflicting results regarding its virilizing action on the female foetus. From some studies, it appears that this hormone causes foetal virilization, especially when used in the first trimester, or stimulation of foetal adrenals with the production of androgens. It also causes anomalies in oestrogenic metabolism in the mother [1, 2, 3, 26, 27, 29, 33]. According to other authors, however, stilboestrol does not have any virilizing effects on the foetus [4, 5, 14, 15]. Administered to 840 pregnant women, a dose of 5–150 mg/day did not produce foetal anomalies [5].

It has been established that a causal relationship does exist between therapy with diethylstilboestrol in pregnancy and adenocarcinoma of the vagina, which develops about 12 years after birth in the daughters of women treated with certain oestrogens [6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27,

28, 37, 38, 39]. Eight cases of adenocarcinoma of the vagina in females of 14–22 years were reported. A retrospective study indicated that seven had been born to women who had taken stilboestrol in the first trimester, while other factors did not seem to be relevant (smoking, radiation during pregnancy, etc.), which might have influenced the growth of tumours [6]. During the period 1950–1970, five cases of adenocarcinoma of the vagina in women under the age of 30 were noted in the State of New York, all born to mothers who had taken oestrogens for threatened abortion. In particular, two had been treated with diethylstilboestrol throughout pregnancy and from 2 weeks to 4 months respectively [7]. In another investigation, 34 women aged from 13 to 24 years were examined. They were the daughters of mothers who had taken the drug before the third month of pregnancy. In these cases, the percentage of vaginal adenositis and vaginal and cervical erosion was 68%, compared to 20% in a control group. It is thus advisable that yearly examination be instituted after the menarche in girls born to women treated with stilboestrol in pregnancy [8].

In 1963–1969, there was an increase over previous years in urogenital tumours. Of these, only mesonephroma of the vagina and of the cervix were correlated with the use of stilboestrol in pregnancy [9]. Of 66 young patients with cervical and vaginal adenocarcinoma, 49 were from mothers treated in pregnancy with stilboestrol, dienoestrol, or hexoestrol. In some cases, the dose administered to the mother did not exceed 1.5 mg/day for a few weeks in the first trimester [11]. In women who had been exposed during the foetal period to the action of stilboestrol administered to the mother, a larger incidence of benign lesions was also encountered compared to controls [12].

Some investigations, however, did not demonstrate an increase in vaginal tumours in young women which could be related to treatment of the mothers with stilboestrol during pregnancy [10].

Recently it has been reported that malformations had occurred in the genito-urinary tract of male foetuses also [35, 36, 40]. A double-blind study conducted over 22 years on 840 women who had taken the drug in pregnancy from the 7th to the 34th week of pregnancy at doses of 5–150 mg/day demonstrated the appearance in male infants of alterations to the genito-urinary tract, including testicular hypoplasia, epididymal cysts, and thickening of the testicular capsule, in a significantly higher proportion than in controls [35]. A retrospective study carried out on the offspring of mothers who had taken stilboestrol from the 20th to the 35th week of pregnancy showed epididymal cysts, testicular hypoplasia, capsular sclerosis, and changes in the sperm. In females, there were menstrual irregularities, a lower incidence of pregnancy, and dysplastic lesions of the vagina and the cervix [36].

From the information reported above, it follows that not only is stilboestrol contra-indicated in pregnancy, but that its use as a 'day after' pill should be carefully evaluated from the point of view of the risk which would arise from a possible pregnancy [13].

In the rat and chick embryo, stilboestrol was teratogenic [30]. In the rat, doses of 10–42 mg from the 12th to the 19th day of pregnancy caused feminization of the male foetus, and anomalies of the genital tract in the female [31].

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Hexoestrol or dihydrostilboestrol

meso-3, 4-di-*p*-hydroxyphenylhexane (MW 270.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C	C	C		

Contra-indicated in pregnancy.

Hexoestrol is a synthetic oestrogen derived from stilboestrol (see page 000), compared to which it is less active.

Administration of hexoestrol in pregnancy should be contra-indicated, since it is related to stilboestrol (see page 113). Of 66 patients with adenocarcinoma of the vagina, 49 were born to women treated with stilboestrol, hexoestrol, or dienoestrol in pregnancy [1].

In the guinea-pig and rabbit, hexoestrol caused abortion at moderate doses, while at higher doses it did not affect the course of the pregnancy [2]. In the guinea-pig, a dose of 1 mg from the 7th to the 10th day of pregnancy, or a dose of 1.5 mg/day from the 8th to the 12th day, caused abortion [3]. At a dose of 2 mg/day, from the 8th to the 12th day, the pregnancy was unaffected [3]. In the rabbit, a dose of 3 mg/day from the 9th to the 14th day of pregnancy had no harmful effects on the pregnancy [3].

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Dienoestrol or dehydrostilboestrol

Hormonfemin, Ortho,

3, 4-di-(*p*-hydroxyphenyl)hexa-2, 4-diene (MW 266.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C	C	C		

Contra-indicated in pregnancy.

Dienoestrol is a synthetic oestrogen with a non-steroid structure, derived from stilboestrol (see page 113), but less active. It is rapidly absorbed orally or subcutaneously.

Occasional references to the use of dienoestrol in pregnancy suggest that it is teratogenic [1], and can cause cancer, with the appearance in adolescence of genital adenocarcinoma in the daughters of women treated with dienoestrol in pregnancy [2]. For this reason, this drug is contra-indicated in pregnancy in the same way as diethylstilboestrol (page 113). Three cases of malformed offspring have been described, with hydrocephalus, meningomyelocele, rachischisis, and pulmonary, hepatic, and intestinal anomalies. The mothers had been treated with dienoestrol at doses of 1.5–6 mg/day during the first trimester of pregnancy [1].

No experimental studies have been described on the use of dienoestrol in pregnancy in laboratory animals.

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Zeranol

3*S*, 7*ξ*-3, 4, 5, 6, 7, 8, 9, 10, 11, 12-decahydro-7, 14, 16-trihydroxy-3-methyl-1*H*-2-benzoxa-cyclotetradecin-1-one (MW 1496.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P	P	P		

To be used with care in pregnancy.

Zeranol is a non-steroid drug with oestrogenic activity, isolated and purified from the fungus *Gibberella zeae*. Because of its trophic action on vaginal epithelium, its ability to inhibit hypophysial gonadotrophin, and its few side effects, zeranol is particularly useful in endocrine disturbances during the menopause and in the post-menopausal period.

Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, zeranol should be used with care in pregnancy because there is insufficient evidence of its complete safety.

In the rat and rabbit, zeranol was not teratogenic. In the rat, doses of 2–6 mg/kg from the 6th to the 15th day of pregnancy caused reduced fertility and an increase in foetal resorptions [1]. In the rabbit, a dose of 1–5 mg/kg during the period of organogenesis did not affect the number or weight of the foetuses compared to controls, and did not cause malformations [1].

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Phosphestrol or stilboestrol diphosphate

diethyl-dioxystilbene diphosphate (MW 472.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C	C	C		

Contra-indicated in pregnancy.

Phosphestrol is a stilbene derivative used mainly in prostatic cancer.

Administration of phosphestrol in pregnancy is contra-indicated because it is a derivative of stilboestrol (see page 113).

No experimental studies have been described on the use of phosphestrol in pregnancy in laboratory animals.

Tamoxifen

Nolvadex,

trans-1-(*p*-dimethylamino-ethoxyphenyl)-1, 2-diphenyl-2-ethylethylene (MW 361.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C	C	C		

Contra-indicated in pregnancy.

Tamoxifen is a triphenyl-ethylene derivative, a chemical analogue of clomiphene. Its *cis*- isomer has an oestrogenic effect, while the *trans* form is anti-oestrogenic in that it reduced cytoplasmic concentrations of protein receptors for oestrogens, which are totally retained within the nucleus of the target cell. Inhibition of responses to oestrogens occurs in the vagina, the uterus, the breast, and in the hypothalamus. Tamoxifen is used in the palliative therapy of oestrogen-dependent neoplasias, in the induction of ovulation in women with oligomenorrhoea or amenorrhoea, in the therapy of menometrorrhage, and in the suppression of lactation. Side effects consist of thrombocytopenia, urinary retention, cephalia, hot flushes, and gastrointestinal disturbances.

The use of tamoxifen to induce ovulation does not give rise to an increase in abortions, but there is a notable increase in gestosis [1] and hypertension.

Although there are no indications for the use of the drug once pregnancy is established, it is contra-indicated because of its inhibitory effects on mitosis and DNA synthesis. This has been confirmed by the manufacturers [2], although there are no clinical data available on this aspect.

No experimental studies have been reported on the use of tamoxifen in pregnancy in laboratory animals.

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Chlorotrianisene

tri-*p*-anisylchloroethylene (MW 380.9)

Chlorotrianisene is a synthetic oestrogen with a non-steroid structure. It has the same actions as oestradiol (see page 106), but it is stored in lipid deposits from which it is slowly released and metabolized to an active oestrogen, probably in the liver. It is administered exclusively by mouth.

Metallenoestrol

β -(6-methoxynaphthyl)- α , α -dimethylvalerianic acid (MW 286.4)

Metallenoestrol is a synthetic oestrogen with a non-steroid structure. It is active orally. For further information on oestrogens in general, see oestradiol (page 106). Metallenoestrol differs from oestradiol in its activity by its lesser effect on breast and endometrial tissue.

Quinoestrol

cyclopentyloxy-19-nor-17 α -pregna-1,3,5(10)-trien-20-in-17-ol (MW 364.5)

Quinoestrol is an oestrogen with analogous properties to those of oestradiol (see page 106). It is absorbed in the gastrointestinal tract, and stored in adipose tissue, from which it is slowly released and metabolized to ethinyloestradiol.

We have been unable to find any information on the use of these drugs in pregnancy in humans or laboratory animals, either in the literature or from the manufacturers. Although no harmful effects have been reported, we maintain that in the absence of reliable information, their use should be contra-indicated in pregnancy and in women of childbearing age who are likely to conceive.

1.4 Progestagens

Progesterone has a specific biological action which facilitates the preparation of the female reproductive tract for pregnancy. Among the numerous synthetic products, so-called gestagens, are various derivatives of the natural hormone.

Some are not suitable for use during pregnancy. The following drugs are discussed in this section:

	Recommendation	Page
Progesterone	NC	120
Hydroxyprogesterone capronate	NC	122
Cyproterone acetate	C	122
Didrogestrone	NC	123
Medroxyprogesterone acetate	NC	124
Allyloestrenol	NC	126
Algestone acetophenide	NC	126
Gestoronone captonate	P	127
Ethisterone	C (C during lactation)	127
Norethisterone	C	128
Ethinodiol acetate	C	130
Chlormadinone acetate	C	131

Progesterone, hydroxyprogesterone, didrogestrone, medroxyprogesterone, allyoestrenol, and algestone are not contra-indicated in pregnancy. However, the use of derivatives of 19-nor-testosterone is contra-indicated because they have a virilizing effect on the female foetus.

Progesterone

pregnene-3,20-dione (MW 314.5)

Not contra-indicated in pregnancy.

Progesterone is synthesized in the ovary, the testes, the adrenal cortex, and in the placenta, starting with pregnenolone, following stimulation by LH or HCG, mediated by cyclic AMP. Progesterone is transformed into 17 α -hydroxyprogesterone which is the precursor of the androgenic hormones (androstenedione and testosterone). These in turn are precursors of the oestrogens (oestrone and oestradiol, respectively). The principal urinary metabolite of progesterone is pregnandiol glucuronate. About 10–20% of the progesterone ingested (in pregnancy this may be 30%) is eliminated unchanged. Progesterone is absorbed in the digestive tract, but is rapidly inactivated in the liver and therefore should be administered parenterally. It has a half life of a few minutes.

The biological effect of progesterone takes place only in the target organs which contain the corresponding cellular receptors. In the cell, it binds to a cytoplasmic protein and is then transported into the nucleus, where it modifies RNA synthesis. The pre-existence of an adequate level of oestrogens increases

the number of progesterone receptors. In the endometrium, progesterone augments proliferative secretion due to oestrogens. Cervical mucus thickens. In the vaginal epithelium, maturation is arrested in the intermediate strata. In the breast there is a proliferation of the acini. In the hypothalamus, progesterone exerts a strong negative feedback which blocks the ovulatory peak of LH. Progesterone inhibits uterine motility by influencing membrane potential and interferes with propagation of contractile stimuli to neighbouring myofibrils, probably by affecting fixation of calcium ions in the membrane. Progesterone also has a thermogenic action, on which basal temperature depends.

In obstetrics and gynaecology, progesterone is used in cases of hyperoestrogenism, in endometrial carcinoma, in suppression of lactation, in threatened abortion, and in premature birth caused by uterine hypercontractility.

Administration of progesterone, as opposed to some synthetic derivatives, in pregnancy does not cause virilization in the female foetus or other malformations [1, 7, 8, 9, 10, 11]. Our own clinical experience is similar, and is based on thousands of cases treated for sufficiently long periods to be able to draw definitive conclusions. Other authors, however, maintain that the synthetic progestagens cause congenital malformations [14, 15]. Cases of virilization of the female foetus have been described after therapy with progesterone [2] or with synthetic progestagens [12, 13] during pregnancy.

In the rat and mouse, progesterone was not teratogenic [3, 4, 5]. In the mouse, doses of 0.25 mg/kg from the 16th to the 19th day of pregnancy did not cause virilization in the female foetus [3]. In the rat, doses of 200 mg/day were not teratogenic [4]. Similar results have been obtained in other studies on the rat [5].

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Hydroxyprogesterone capronate or hexanoate

Proluton Depot, 17 α -hexanoylpregnene-3, 20-dione (MW 428.6)

Not contra-indicated in pregnancy.

Hydroxyprogesterone is a synthetic progestagen with a delayed action, weakly androgenic, and without oestrogenic activity. It is used in gynaecology in the therapy of threatened abortion.

Hydroxyprogesterone has no virilizing effect on the female foetus, and we would concur with this view, as do other studies [1, 2, 3, 4, 5, 6, 7, 8, 10]. In 43 pregnant women, the drug was administered once per week at a dose of 250 mg/day intramuscularly for threatened premature birth. The mean duration of the pregnancy was 38.6 \pm 1.4 weeks, and no anomalies in the foetuses were noted [10]. In a 5-year retrospective study on 120 pregnant women treated with hydroxyprogesterone at a dose of 250 mg/week, no undue consequences in female foetuses were observed [7]. In 1500 infants born to patients treated with hydroxyprogesterone only two had clitoral enlargement [8]. The infant of a patient who had taken didrogesteron in pregnancy by the oral route at a dose of 20 mg/day from the 8th to the 20th week, and then 10 mg/day until term, together with hydroxyprogesterone hexanoate at a dose of 250 mg/week intramuscularly from the 8th to the 20th week had multiple malformations of the genito-urinary tract [11].

In the rat, hydroxyprogesterone did not cause virilization in the female foetus [9].

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Cyproterone acetate

Androcur, 17-acetoxy-6-chloro-1 α , 2 α -methylenepregna-4, 6-diene-3, 20-dione

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Cyproterone acetate is a derivative of hydroxyprogesterone and has anti-androgenic, progestinic and antigonadotrophic actions. Its anti-androgenic action involves inhibition of formation of the complex between androgen and receptor in the nucleus, and a displacement of androgens from cytoplasmic receptors, as well as inhibition of testosterone synthesis in the Leydig cells. Cyproterone caused a dose-dependent inhibition of spermatogenesis, reduces the volume of the ejaculate, retards maturation of the skeleton, and causes sedation and a tendency towards psychic depression. Therapeutic uses include hirsutism, acne, seborrhoea, androgen-dependent alopecia, and benign and malignant neoplasias of the prostate. The reversible block of spermatogenesis induced by cyproterone acetate has led to its investigation as a male contraceptive. However, the effects on loss of libido in the male are controversial. Side effects of cyproterone acetate include, in the woman, appearance of menstrual irregularities, and in the male, gynaecomastia with eventual galactorrhoea, and loss of libido. Cyproterone is contra-indicated in the presence of diabetes, chronic liver disease, and anaemia.

Administration of cyproterone in pregnancy is contra-indicated because of known interference in foetal sexual differentiation [1, 2]. For this reason, simultaneous administration of oestrogens is recommended at doses sufficiently high to lead to contraception.

In the rat, mouse, and rabbit, cyproterone crossed the placental barrier [3]. Administered at various stages of pregnancy, it provoked intense feminization of the male foetus, together with 'testicular feminization' in the male. It is known that the cause of this type of intersexuality rests upon a lack of sensitivity to the androgens [3, 4, 5, 6, 7].

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Didrogesterone or isopregnenone

6-dehydro-9 β , 10 α -progesterone (MW 312.5)

Not contra-indicated in pregnancy.

Didrogesterone is a progestagen derived from retroprogesterone. It has properties similar to those of the natural hormone, but is not hyperthermic and is active orally. It has no androgenic or oestrogenic activity, and does not inhibit ovulation. Didrogesterone differs structurally from progesterone as

regards the steric position of the groups in positions 9 and 10, which are inverted in relation to the plane of the molecule.

Didrogesterone is used for the same indications as progesterone, but it has the advantage of being more active orally.

Administration of didrogesterone in pregnancy has no embryofoetotoxic or teratogenic effects, and in particular, there have been no reports of virilizing effects on the female foetus [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Our own clinical experience supports this view. Administered at various stages of pregnancy, didrogesterone at doses of 10–60 mg/day did not have virilizing effects on the female foetus [10, 11]. The infant of a patient who had taken the drug in pregnancy orally at a dose of 20 mg/day from the 8th to the 20th week, and then 10 mg/day until term, together with hydroxyprogesterone hexanoate at a dose of 250 mg/week intramuscularly from the 8th to the 20th week had multiple malformations of the genito-urinary tract [14].

In the rat, didrogesterone has no embryofoetotoxic or teratogenic effects [12, 13]. In ovariectomized rats, the drug at oral doses of 10 mg from the 14th to the 20th day of pregnancy was able to maintain the pregnancy without side effects, and with subsequent birth of normal foetuses [12].

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Medroxyprogesterone acetate

Depo-provera, Provera,

6 α -methyl-3, 20-dioxopregn-4-en-17 α -yl acetate (MW 386.5)

Not contra-indicated in pregnancy.

Medroxyprogesterone has an activity similar to that of progesterone, but with more pronounced progestational and inherent ovulatory effects. It is active orally and intramuscularly, in aqueous suspension, and has a prolonged action. It is free from androgenic or oestrogenic activity, and is used in both obstetrics and gynaecology.

Medroxyprogesterone is widely used in pregnancy, and there have been no reports of harmful effects on the foetus. Our own clinical experience confirms

this view. In 175 pregnant women treated with total doses of 240–560 mg, particularly in the first trimester, the drug did not cause virilization of the female foetus [1]. In 207 cases treated with initial doses of 15–20 mg/day for 8 days, followed by 5–10 mg for 30 days or 50 mg for 3 days, and then 10 mg for at least 15 days, during the first trimester, there were no side effects in the foetus [2]. In 19 patients medroxyprogesterone was administered at a dose of 100 mg/week from the 1st to the 20th week, and then at doses of 50 mg/month for the rest of pregnancy. This did not cause virilization in the female foetus [3]. In 100 patients, medroxyprogesterone at doses of 50 mg/week from the 16th to the 22nd week (therapy was prolonged until the 36th week in some cases) did not cause side effects in the foetus [4]. In 98 cases treated with 40–60 mg/day orally in the first 2 months of pregnancy, there were no effects on the foetus [5], and another 210 women treated with the drug gave birth to healthy infants [6]. In 30 pregnant women treated with medroxyprogesterone (30 mg/day for 1 week) in the first trimester, 13 gave birth to female foetuses, none of whom had any genital malformations [7]. Of 172 patients treated first during the 12th week of pregnancy with 5–50 mg/day, only one gave birth to an infant with transient clitoral hypertrophy [8]. In another series of cases, 50 pregnant women treated with medroxyprogesterone (total dose of 100–1120 mg) produced healthy infants [9].

Despite these data, the Italian Ministry of Health and the United States Food and Drug Administration advised against the use of medroxyprogesterone in pregnancy because the teratogenic effects had been insufficiently investigated. We list this fact for completeness, but we believe that there is no basis for such a prohibition.

In the rat, overall doses of 1–20 mg medroxyprogesterone from the 16th to the 19th day of pregnancy produced virilization in the female foetus [10]. Similar results were obtained by other authors [11]. A dose of 1 mg given subcutaneously from the 15th to the 20th day caused virilization of the female foetus [12]. A subcutaneous dose of 0.1–2.5 mg/kg from the 16th to the 20th day caused an increase in the anogenital distance in the male offspring [13].

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Allylestrenol

Gestanon, 17 α -allyloestren-17-ol (MW 300.5)

Not contra-indicated in pregnancy.

Allylestrenol is a synthetic progestagen which forms part of the oestrenol group. These substances are derived from norethisterone by removal of the oxygen atom in position 3. Their biological activity depends critically on the substituents at position 17. Allylestrenol has principally progestational effects and is not androgenic or oestrogenic. It is active orally.

Allylestrenol administered in pregnancy is neither embryofoetotoxic nor teratogenic, and does not provide virilizing effects in the female foetus [1,2, 3, 4,5,6,7]. Our own clinical experience supports this view. Administration of the drug in 15 patients at oral doses of 15–30 mg/day for 5–7 days during various stages of pregnancy did not cause virilizing effects in the female foetus [6]. Administration to 20 patients for 7 days at oral doses of 15 mg/day from the 2nd to the 5th month of pregnancy did not provoke virilizing effects on the female foetus [7].

In the rat, administration of allylestrenol at doses of 5–15 mg/day on the 19th day of pregnancy did not cause embryofoetotoxic or teratogenic effects, or provoke virilization in the female foetus [4,8].

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Algestone acetophenide

16 α , 17 α -(1-phenylethylidenedioxy)pregnene-3, 20-dione (MW 448.6)

Not contra-indicated in pregnancy.

Algestone is a synthetic progestagen which has an action equal to that of progesterone. It is also active orally. If administered intramuscularly, it is slowly dispersed, acting as a depot preparation. Algestone is also used in gynaecology in disturbances of the menstrual cycle, and, in association with a depot oestrogen, as a contraceptive. It is used in obstetrics in threatened abortion.

There have been no reports of virilizing effects related to the use of algestone in pregnancy [1,2]. Algestone was administered to 13 pregnant women with threatened abortion, with no side effects in the foetus [2].

In the rat, subcutaneous doses of 2.5–10 mg/kg from the 14th to the 19th day of pregnancy did not cause any sexual changes in either male or female foetuses [3,4]. A subcutaneous dose of 10 mg/kg from the 8th day of pregnancy

in ovariectomized rats maintained the pregnancy without harmful effects on the foetus. Subcutaneous doses of 1–4 mg/kg or oral doses of 15 mg/kg in the first stage of pregnancy did not affect implantation or foetal development [5].

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Gestonorone capronate or gestronol

17 α -hydroxy-19-norpregnen-3, 20-dione capronate (MW 414.6)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Gestonorone is a long-acting progestagen which is used in the treatment of endometrial carcinoma and prostatic hypertrophy. It is not usually administered during pregnancy.

Gestonorone has been used in pregnancy to treat threatened abortion during the first trimester, without side effects on the foetus [1].

In the rat, doses of 10–30 mg/kg from the 16th to the 21st day of pregnancy given subcutaneously provoked no harmful effects in the foetus [1]. On the basis of such results, some authors conclude that this hormone may be administered at high doses in pregnancy, since there is no virilization of the female foetus [1]. Others, however, express the contrary opinion that gestonorone is contra-indicated in pregnancy [2, 3].

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Ethisterone or ethinyltestosterone or pregneninolone

17-hydroxy-17 α -pregnen-20-in-3-one (MW 312.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		C

Contra-indicated during pregnancy and during lactation.

Ethisterone is a synthetic product, active orally, with progestational activity as well as being oestrogenic and androgenic. It was widely used in the treatment of threatened abortion, but has now been completely abandoned in obstetrics.

Ethisterone caused virilization of the female foetus when taken in pregnancy, and in particular, when taken in the first few weeks, produced serious hermaphroditism. Administered at later stages, it caused only clitoral hypertrophy without sealing of the vaginal labia majora [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 17]. In seven cases treated with ethisterone at an oral dose of 30–100 mg/day from the 4th week of pregnancy until term, there were varying degrees of virilization in female fetuses [10]. In eight cases treated with ethisterone at oral doses of 30–250 mg/day from the 4th to the 36th week of pregnancy, there were virilizing effects in the female foetus [11]. One pregnant woman treated with an oral dose of 10 mg/day from the 4th to the 28th week gave birth to an infant with marked signs of virilization [12]. Administration to 34 patients of oral doses of 20–250 mg/day at various stages of pregnancy caused the appearance of clear signs of virilization in the infants [15].

Ethisterone passes into breast milk, and is contra-indicated during lactation because it causes acceleration of bone growth in the infant [18].

In the rat and rabbit, ethisterone administered in pregnancy had a virilizing effect on the female foetus [1, 9, 13, 14, 16].

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Norethisterone or norethindrone acetate

Ortho-Novin, Anovlar 21, Utovlan, etc.,

17-hydroxy-19-nor-17 α -pregene-20-in-3-one (MW 298.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

After the synthesis of ethisterone (17α -ethinyltestosterone), the first orally active progestagen, it was discovered that the derivatives of testosterone which lacked a methyl group in position 19 were much more effective, especially if there was also an alkyl group in position 17. Thus, norethisterone was synthesized. It was a progestagen, active orally, and with more marked androgenic properties than ethisterone.

The use of norethisterone in pregnancy is contra-indicated by many authors, because of its possible virilizing effects on the female foetus [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. In nine pregnant women administration of norethisterone at doses of 5–40 mg/day orally at periods varying from the 5th to the 36th week caused virilizing effects in the female foetus [10]. Administration to three patients of oral doses of norethisterone from 5–30 mg/day between the 2nd and the 7th month of pregnancy caused the appearance of virilization in female foetuses [11]. Other studies have also demonstrated that oral administration of the drug in doses of 10–30 mg/day at various stages of pregnancy caused slight virilizing effects [12].

On the contrary, other authors have reported that use of norethisterone in pregnancy did not produce any side effects in the foetus [13, 14]. In a 5-year retrospective study, administration of norethisterone to 25 patients at a dose of 5 mg three times a day at various stages of pregnancy had no harmful effects [3]. Ninety pregnant women treated with norethisterone at doses of 20 mg/day for the first 5 days, 10 mg/day for a further 5 days, and 5 mg/day as a maintenance dose until term, gave birth to normal female infants [14].

In the mouse and rabbit, the effects of norethisterone in pregnancy were controversial [1, 15]. Administration of the drug at varying doses at different stages of gestation caused virilization of female foetuses [1]. In the rabbit, oral doses of norethisterone, 1–30 mg/kg, from the 8th to the 20th day of pregnancy caused a significant increase in foetal resorption but was not teratogenic, since surviving female foetuses were normal [15]. In the mouse, oral doses of 1–10 mg/kg from the 8th to the 15th day of pregnancy produced cleft palate but did not cause virilization [15].

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Ethinodiol acetate

3 β , 17-diacetoxy-19-nor-17 α -pregnen-20-in (MW 384.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Ethinodiol is similar to norethisterone (see page 128), but is more potent. It is used in association with an oestrogen, for example mestranol, in oestrogen-progestagen therapy.

Although there have been no reports of harmful effects on the human foetus, the mother, or the pregnancy, ethinodiol is contra-indicated because it is a derivative of testosterone (see page 90).

In the rat and rabbit, ethinodiol prevented the initiation of pregnancy, but once pregnancy was established it was neither embryofetotoxic nor teratogenic [1]. In the rat, subcutaneous doses of 0.63 mg/kg or oral doses of 3 mg/kg from the 1st to the 7th day of pregnancy reduced the number of pregnancies by 50%. Subcutaneous doses of 2–5 mg/kg or oral doses of 5 mg/kg from the 2nd to the 4th day of pregnancy, and doses of 5 mg/kg on the 1st day produced the same effect. A dose of 0.2 mg/kg from the 1st to the 18th day of pregnancy, a dose of 0.4 mg/kg from the 7th to the 18th day of pregnancy, a dose of 0.5–2 mg/kg from the 1st to the 21st day, or a dose of 0.5–1 mg/kg throughout pregnancy did not produce teratogenic effects [1].

In the rabbit, subcutaneous doses of 0.1 mg/kg from the 10th day of pregnancy had no side effects on the pregnancy, while doses of 0.25–0.5 mg/kg caused abortion. A subcutaneous dose of 0.1–1 mg/kg caused abortions. An oral dose of 1–2 mg/kg from the 1st to the 28th day and from the 5th to the 28th day of pregnancy, and 0.01–0.1 mg/kg throughout pregnancy produced no

teratogenic effects [1].

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Chlormadinone acetate

17 α -acetoxy-6-chloropregna-4,6-diene-3,20-dione (MW 404.9)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Chlormadinone is a synthetic progestagen with weak oestrogenic activity. It is derived from 19-nortestosterone, and is used as a contraceptive in combination with mestranol, principally in sequential preparations. High doses are used in the treatment of endometrial carcinoma.

No definite reports of virilization have been found. Some authors believe that chlormadinone has no harmful effects on the foetus or the offspring [1, 2]. However, the drug is contra-indicated in pregnancy because it is a derivative of 19-nortestosterone. In 146 pregnant women, chlormadinone was used at doses of 2–50 mg/day at various stages of pregnancy. There were four cases of intra-uterine death (of which one was malformed and three had hypospadias, cleft palate, and inguinal hernia respectively), and five cases of neonatal death. The pregnancies treated, however, were classified as high risk, and so intra-uterine and neonatal death could be due to factors other than drug administration [1]. At doses of 2–4 mg/day from the 60th to the 75th day of pregnancy, chlormadinone did not produce malformations of the genital tract [2].

In the mouse, rat, and rabbit, chlormadinone caused teratogenic effects only at doses higher than therapeutic, and did not have virilizing effects. On the basis of experiments on rats, the hypothesis has been advanced that this may be attributed to the double bond in position 6 and to substitution of a chlorine atom instead of a methyl group, also in position 6 [3, 4, 5, 6, 7]. In the mouse, oral doses of 1–50 mg/kg at various stages of gestation caused cleft palate, but not virilization [4]. In the rat, subcutaneous doses of 0.1–10 mg/kg from the 14th to the 20th day caused no malformations of any type [5]. At doses of 4–40 mg/kg there were again no side effects, but doses of 60 mg/kg caused slight virilization [6]. Intramuscular doses of 1.5–6 mg/day or oral doses of 6–36 mg/day on the 8th or the 14th days of pregnancy were not teratogenic [7].

In the rabbit, oral doses of 1–10 mg/kg from the 8th to the 20th day of pregnancy produced aplasia of the abdominal wall and cleft palate, but

not virilization [4]. Subcutaneous doses of 0.2–0.3 mg/day or oral doses of 0.5–1.5 mg/day, after the 8th day of pregnancy, had no effect on foetal sexual characteristics, and were not teratogenic [7]. In all cases, doses which caused malformations were considerably higher than therapeutic.

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1.5 Oral oestrogen-progestagen combinations

Contra-indicated in pregnancy.

It is known that peripheral hormones have both a replacement function and a hypothalamic inhibiting effect. For that reason, the oestrogen-progestagen combination has been used for some years to produce conditions in the endometrium which cause an 'artificial' form of menstruation. The possibility of inhibiting the production of gonadotrophic hormones with these drugs has been studied with the aim of suppressing ovulation. When progress in the synthesis of steroid hormones had reached the point which enabled drugs with a more powerful inhibitory action on the gonadotrophins, and only slight effects on the receptors in the reproductive tract, to be produced, the oestrogen-progestagen combinations were investigated and marketed commercially as contraceptives.

In these products, there is a potentiating effect between the oestrogenic and the progestagenic components in their action on the hypothalamus, which results in a certain 'antagonism' towards peripheral effects (the high dose 'pill' combination). Later it was seen that much lower doses produced equally effective contraception, based mainly on peripheral mechanisms and less on gonadotrophic inhibition (the low dose 'pill').

The intention of reproducing parapsychological endometrial changes has resulted in the introduction of 'sequential' combinations (the 'sequential' pill). The contraceptive effect in these cases does not show potentiation between the two types of steroids which occurred in high dose combinations, and produced increased side effects.

When a doctor prescribes oral contraceptive therapy, he must establish first whether there are contra-indications on the basis of obstetric and gynaecological conditions, other illness, or laboratory reports. The most common contra-indications are: liver disease (in particular, steroid jaundice), thrombophlebitis, phlebothrombosis, precancerous lesions of the reproductive tract, hypophyseal dysfunction, obesity, vasomotor disturbances, otosclerosis, epilepsy, diabetes,

hypertension, and lactation. The following side effects may occur: nausea, vomiting, weight increase, breast tenderness, psychic depression, breakthrough bleeding, amenorrhoea, and hepatocellular damage.

Oestrogen-progestagen combinations given orally may be used as a pregnancy test by provoking menstruation, as contraceptives, and with the additional aim of substitution therapy. The following are commonly used:

Progestagen component	Oestrogen component	Proprietary name
Norethisterone (0.5 mg)	Ethinylloestradiol (50 μ g)	Anovlar 21
Norethisterone (0.5 mg)	Ethinylloestradiol (35 μ g)	Brevinor
Ethynodiol diacetate (2 mg)	Ethinylloestradiol (30 μ g)	Conova
Ethynodiol diacetate (500 μ g)	Ethinylloestradiol (30 μ g)	Demulen
Levonorgestrel (250 μ g)	Ethinylloestradiol (30 μ g)	Eugynon 30
Norethisterone acetate (3 mg)	Ethinylloestradiol (50 μ g)	Gynovlar 21
Norethisterone acetate (1 mg)	Ethinylloestradiol (20 μ g)	Loestrin
Levonorgestrel (50 μ g)	Ethinylloestradiol (30 μ g)	Logynon
Lynoeestrenol (2.5 mg)	Ethinylloestradiol (50 μ g)	Minilyn
Norethisterone acetate (1 mg)	Ethinylloestradiol (50 μ g)	Minovlar ED
Norethisterone (1 mg)	Ethinylloestradiol (35 μ g)	Norimin
Norethisterone (1 mg)	Mestranol (50 μ g)	Norinyl-1
Norethisterone acetate (2.5 mg)	Ethinylloestradiol (50 μ g)	Norlestrin
Norethisterone acetate (2.5 mg)	Ethinylloestradiol (50 μ g)	Orlest
Norethisterone (1 mg)	Mestranol (50 μ g)	Ortho-Novin
Levonorgestrel (250 μ g)	Ethinylloestradiol (50 μ g)	Ovran
Ethynodiol diacetate (1 mg)	Ethinylloestradiol (50 μ g)	Ovulen
Norethisterone (500 μ g)	Ethinylloestradiol (35 μ g)	Ovysmen
Levonorgestrel (50 μ g)	Ethinylloestradiol (30 μ g)	Trinordial

Oestrogen-progestagen ingestion during pregnancy, whether established or presumed, is always an accidental event, due to failed induction of menstruation or to an error in contraceptive therapy. This may occur as a result of an error in the interpretation of the instructions for use, supplied with the preparations, which advise the patient not to interrupt use of contraceptives, even if this is used in a discontinuous way, when menstruation does not appear. In these cases, the oestrogen-progestagen combination taken in the embryonic period often

causes teratogenic effects which are widely described in the literature [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 17, 24, 25, 28, 29].

In 1967, the first references were published on the increased incidence of malformations of the central nervous system (myelomeningocele) in the offspring of mothers subjected to pregnancy tests involving the administration of oestrogen-progestagen combinations in high doses [1]. At that time, a syndrome of polymalformations was defined, and designated 'VACTERL' (vertebral, anal, cardiac, tracheal, oesophageal, renal, limb involvement) in the infants of women who had taken the oestrogen-progestagen combination in the first trimester [6]. Nineteen cases of VACTERL were studied. It was not always possible to state exactly the type and dose of the combination used in the pregnancy test [9, 17].

Administration of oestrogen-progestagen combinations as a pregnancy test should be discontinued, in our opinion, because of possible serious side effects. This conclusion has also been reached by other authors [18, 19, 23], as well as by official English and American organisations [8, 15, 16, 20]. The Ministry of Health in Italy has expressed the same opinion [26].

In the rat and rabbit, administration of oestrogen-progestagen combinations (ethinodiol diacetate and mestranol) at different stages of pregnancy had no embryofoetotoxic or teratogenic effects [21, 22]. More recent studies [27] have demonstrated a teratogenic effect in the rat.

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2. HYPOPHYSIAL HORMONES

Those products extracted from the hypothalamus/hypophysis, and related drugs, are discussed in this chapter. They include the two octapeptides from the hypothalamus (oxytocin and vasopressin [ADH]), adeno-hypophysial and analogous trophins (ACTH, tetracosactrin, PMSG, HCG, HMG, PRL, STH, TSH), two synthetic products with completely different chemical structures which have a competitive action on hypothalamic receptors for oestrogens, and lastly, para-oxypropiophenone, an inhibitor of gonadotrophin. These are listed below:

	Recommendation	Page
Oxytocin	C (P during labour)	136
Antidiuretic hormone (ADH)	C	138
Adrenocorticotrophic hormone (ACTH)	P	139
Tetracosactrin	P	141
Pregnant mare serum gonadotrophin (PMSG)	NC	142
Human chorionic gonadotrophin (HCG)	NC	142
Human menopausal gonadotrophin (HMG)	NC	143
Prolactin (PRL)	NC	143
Somatotrophic hormone (STH)	NC	144
Thyroid stimulating hormone (TSH)	NC	145
Clomiphene citrate	C	147
Cyclofenil	C	149
Para-oxypropiophenone	P	150

The use of oxytocin is advisable only during labour under strict medical control. Antidiuretic hormone is contra-indicated in pregnancy. Corticotrophin and tetracosactrin should be used with care. The gonadotrophins PMSG and HCG are not contra-indicated. Gonadotrophin, HMG, prolactin, somatotrophin, and thyrotrophin have no therapeutic use in pregnancy. Clomiphene and cyclophenyl are contra-indicated because of possible teratogenic effects. Para-oxypropiophenone should be used with care.

Oxytocin

Syntocinon, Syntometrine (MW 1007.23)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C	P	
Chronic					

Contra-indicated in pregnancy and should be used with care in labour.

Oxytocin is an octapeptide produced by the paraventricular nuclear cells of the hypothalamus. It migrates along the axons of these cells and reaches the perivascular nerve terminals of the neurohypophysis, where it accumulates, bound to proteins, in the form of neurosecretory granules. A sensory stimulus coming from the vagina, the cervix, or the breast can cause the release of oxytocin by a reflex route, but only one fifth of that contained in the neurohypophysis can rapidly enter the circulation.

Oxytocin causes the contraction of the smooth muscle of the uterus and the mammary myoepithelial cells (milk ejection). The contractile response of the non-gravid uterus depends upon the phase of the menstrual cycle. In pregnancy, it depends on the gestational age. It increases eight-fold from the 20th to the 36th week, and then remains the same until the initiation of labour. It is conditioned by oestrogen and progesterone levels, and individual sensitivity. In small doses, oxytocin reproduces the normal uterine contractile pattern of labour, with the exception of a slight tendency towards increased basal tone, which does not affect foetal oxygenation. At higher doses, oxytocin causes uterine tetany which lasts for about 5–10 minutes.

Oxytocin at high doses relaxes the smooth muscle of the blood vessels and thus lowers arterial pressure, especially diastolic. This is particularly evident during general anaesthesia. However, prolonged administration can cause hypertension.

The structural similarity of oxytocin to ADH results in the production, at high doses, of water retention, and fatal cases have been described [1, 2, 3, 4].

Oxytocin is digested by gastric enzymes and therefore must be administered by the parenteral, buccal, or intranasal routes. It has a plasma half life of a few minutes, which is shortest during the last stage of pregnancy and during lactation. This is primarily attributed to the plasma proteolytic enzyme oxytocinase, or cystine-amino peptidase, produced by the placenta.

It is believed that oxytocin is physiologically more important for completion of labour and for the prevention of post-partum haemorrhage than for the initiation of labour [5, 8], which is apparently linked to prostaglandins [6].

Oxytocin is contra-indicated in the presence of EPH-gestosis, past hysterectomy, serious cases of mechanically assisted birth, or foetal distress. In patients treated with antihypertensive drugs, oxytocin can produce serious hypertension.

Some authors describe an increase in neonatal bilirubin when the mother has received oxytocin to induce labour, although normal amounts of bilirubin have been reported when the mothers received oxytocin only to complete the birth. Such hyperbilirubinaemia, however, may not be related with certainty to the use of oxytocin [7].

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Antidiuretic hormone (ADH) or vasopressin or argipressin

(MW 1084.11)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antidiuretic hormone is an octapeptide which controls the osmotic pressure of organic liquids by modulating the permeability of the nephron (distal tubule) to water. Its mechanism of action is via activation in the tubule of the enzyme adenylyl cyclase, which causes an increase in the cellular content of cyclic AMP. The presence of arginine or lysine (in pig hormone) in position 8 is essential for this antidiuretic action. There is a distinction between arginine-vasopressin and lysine-vasopressin (lipressin), which are both obtained by synthesis. The presence of isoleucine in position 3 is essential for the activity of ADH as it is for oxytocin (see page 136). ADH, like oxytocin, is synthesized in the supra-optic and paraventricular nuclei and is stored preformed, being released by the stimulus of hyperosmolarity following dehydration or serious haemorrhage.

The pressor effect of ADH is due to the generalized vasoconstriction caused by direct action on contractile elements. The action of the hormone on smooth muscle is observable in both the uterus and the intestine.

Oral administration of ADH and lipressin results in rapid inactivation by the enzyme trypsin which splits the link between arginine and glycine. The hormone is absorbed to a small extent through the nasal mucosa. ADH is used

in the diagnosis and treatment of diabetes insipidus, but should not be used as a pressor agent, in spite of its alternative name of vasopressin. In women, it may cause the appearance of spastic uterine contractions similar to those of algomenorrhoea.

Administration of high doses of ADH during pregnancy can cause contractions of the uterus, despite the presence of a plasma peptidase similar to oxytocinase which splits the link between cystine and tyrosine in the ADH molecule. The harmful effects on foeto-placental circulation caused by ADH should not be dismissed.

In the rat, ADH injected into the amniotic sac caused malformations of the limbs [1].

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Adrenocorticotrophic hormone (ACTH) or corticotrophin

Acthar (MW 4567.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Corticotrophin is a polypeptide containing 39 amino acids, and it produces hyperplasia in the adrenal cortex, an increase in hydrocortisone stores, and an increase in androgens. Corticotrophin has no marked effect on storage of aldosterone, which proceeds independently of the hypophysis.

ACTH release is regulated by a negative feedback controlled by cortisol and corticosterone, as well as by the stimulus caused by circulating adrenaline. In the median eminence, CRH (corticotrophin releasing hormone) is synthesized. This hormone reaches the adenohypophysis via the hypophysial portal system and causes the release of ACTH by the basophil cells. Some physiopathological conditions, such as surgical intervention, birth, frostbite, fatigue, and other forms of stress can increase ACTH release within a few minutes. The plasma half life of this hormone is about 15 minutes, because it is rapidly inactivated in the tissues.

ACTH increases the synthesis rather than the release of the adrenocortical hormones. It stimulates the enzyme adenylyl cyclase in the membrane of the adrenal cells, thus accelerating the synthesis of cyclic AMP. This in turn

stimulates the initial oxidative reaction of steroidogenesis, which breaks the side chain of cholesterol and leads to the formation of pregnenolone, as well as being responsible for the trophic effect on the adrenal cortex. ACTH is used diagnostically for tests of adrenocortical function and therapeutically in asthma, delirium tremens, herpes zoster, multiple sclerosis, myasthenia gravis, and rheumatoid arthritis. Treatment with ACTH causes an increase in glucocorticoids in the body, as well as mineralocorticoids and androgens. The latter effects do not occur when glucocorticoids are administered alone.

No agreement has yet been reached regarding the effects of ACTH on the foetus during pregnancy. Some authors believe that the hormone is better tolerated than cortisone, and has no harmful effects [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 20, 33, 34]. No side effects were observed in the infant of a patient treated for a long period with ACTH for acute articular rheumatism [2]. A pregnant woman was treated for hyperemesis with ACTH during the second trimester with initial doses varying between 60–80 mg/day and 20 mg/day until term, with no harmful effects on the foetus [6]. In another case, treatment of herpes gestationes with cortisone at doses of 50–100 mg/day from the 28th to the 32nd week, and then with ACTH at a dose of 60 mg/day, produced no side effects on the foetus [7]. A patient treated for rheumatic fever with 100 mg/day ACTH from the 36th week until term gave birth to a normal infant [8]. Twenty-five pregnant women with hyperemesis were treated with ACTH at a dose of 10 IU/day for cycles of 2–4 days in the first trimester without harm to the foetus [10]. A patient with lupus erythematosus was treated with cortisone and ACTH throughout pregnancy with no harmful effects on the foetus [13].

Some authors, however, believe that ACTH is contra-indicated in pregnancy both because of possible teratogenic effects [16, 17, 18, 32] and because of a possible hypoadrenalism resulting from overstimulation of the maternal adrenals [15, 19, 35]. In 57 women treated with ACTH there was one reported abortion, one death of a premature infant, and one malformed infant [16]. In 428 patients treated with corticosteroids or ACTH in pregnancy, there were 11 abortions, 12 premature births, 3 cases of adrenal insufficiency, and 11 malformed infants [16]. From a retrospective study on 260 pregnant women treated with ACTH before the 14th week, there were two malformed neonates and an increase in the number of foetal deaths [17].

In the rat, mouse, rabbit, and macaque mulatto, corticotrophin was embryo-foetotoxic and teratogenic [18, 22, 23, 24, 25, 26, 28, 29, 30, 31]. It provoked premature birth in sheep [21]. In the mouse, at doses of 5 mg every 6 hours from the 13th to the 15th day of pregnancy, it caused cleft palate, and similar results were obtained in other studies [23]. In the macaque mulatto, doses of 20 mg/day from the 17th to the 67th day of pregnancy caused hypoplasia of the foetal adrenals [27].

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Tetracosactrin

Synacthen (MW 2933.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Tetracosactrin is a synthetic polypeptide formed from the first 24 of the 39 amino acids which make up human corticotrophin. It has the same properties and clinical, diagnostic, and therapeutic applications as ACTH (see page 139).

***Pregnant mare serum gonadotrophin (PMSG) or
follicle-stimulating serum gonadotrophin***

Not contra-indicated in pregnancy.

PMSG is a glycoprotein produced from pregnant mare placenta. It has an action which is more powerful on follicle stimulation than luteinization. As opposed to other gonadotrophins, it is not eliminated in the urine, and has a prolonged effect.

PMSG has been used for several decades in the treatment of threatened abortion with no embryofoetotoxic or teratogenic effects.

No experimental studies have been described on the use of PMSG in pregnancy in laboratory animals.

Human chorionic gonadotrophin (HCG)

Pregnyl, Profasi (MW 30 000)

Not contra-indicated in pregnancy.

HCG is a glycoprotein made up of two subunits: alpha, essentially identical to that of LH, and of hypophysial TSH; and beta, similar to that of LH, but with different immunological reactivity. It is produced by the placenta and appears in the blood and urine of pregnant women. It appears to function by stimulating the pregnant corpus luteum, and before that, the foetal adrenals produce dehydroepiandrosterone, the precursor of the oestrogens. HCG also has an immunosuppressive action. In the non-pregnant state, the action of HCG is apparently identical to that of LH, that is, it stimulates the synthesis of cyclic AMP to initiate steroidogenesis in ovarian and testicular target cells. The prostaglandins also collaborate in producing an increase in cyclic AMP induced by LH/HCG, and are thus determining factors in the subsequent ovarian response. In fact, by inhibiting the biosynthesis of the prostaglandins, ovarian hyperstimulation may be prevented.

HCG is used during pregnancy in the prevention and treatment of threatened abortion, and prurigo gestationis [1]. No embryofoetotoxic or teratogenic effects have been reported. An elevated level of HCG, as in multiple pregnancies, has no adverse effects on the foetus.

In the rat, HCG prolonged pregnancy and caused foetal macrosomia [2,3,9]. In the sheep, on the other hand, administration of HCG at various times during pregnancy had no effects [5]. In the rabbit and guinea-pig, HCG caused regression of the corpus luteum [6]. In the mouse, it produced foetal malformations [8]. In the rabbit, administration of HCG on the 9th day of pregnancy caused degeneration of the corpus luteum [6], and doses of 10 000–80 000 IU from the 20th to the 25th day of pregnancy caused increased size of foetal gonads [7].

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***Human menopausal gonadotrophin (HMG) or
follicle-stimulating human gonadotrophin or menotrophin***

Pergonal (MW 17 000—34 000—68 000)

Not contra-indicated in pregnancy.

HMG is a gonadotrophin, extracted from the urine of women in menopause, and has a mainly follicle-stimulating action. It is used in association with chorionic gonadotrophin or with clomiphene to induce ovulation. In the male, it stimulates testicular maturation. A very high dose can cause ovarian hyperstimulation, multiple ovulation, ascites, arterial thrombosis, hypovolaemia, and even death. Therapy therefore needs to be monitored with the daily dose of oestrogens.

HMG is used in the treatment of anovulatory sterility, with frequent success. Some authors refer to a small incidence of multiple pregnancies and of foetal malformations, after ovarian hyperstimulation [1, 2]. The drug has no therapeutic value in pregnancy.

In 36 pregnancies which occurred after treatment of 263 patients with HMG + HCG, there were 5 cases of multiple pregnancies, 9 abortions, and one foetal malformation [1]. In another report, 68 patients with longstanding sterility were treated with ANG + HCG, and in two cases with HMG + clomiphene. There were 10 cases of ovarian hyperstimulation, with the birth of 3 infants with major malformations. There were also frequent multiple pregnancies, including 23 sets of twins, 5 of triplets, 2 of quadruplets, and one of sextuplets. The incidence of abortion was 29%, and of perinatal death 27% [2].

No experimental studies have been found on the use of HMG in pregnancy in laboratory animals.

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Prolactin (PRL)

(MW 25 000 for sheep)

Not contra-indicated in pregnancy.

Prolactin is an hypophyseal protein hormone which stimulates the development of the mammary glands (ducts and alveoli) after suitable oestrogenic and progestagenic preparation. Prolactin also induces the synthesis in the endoplasmic reticulum and the Golgi apparatus in the alveolar cells of the proteins and glucides in milk. The production of prolactin is constant in humans. It normally increases in a progressive way during pregnancy. In the puerperium it increases 10–100 times within 30 minutes of suckling, or manipulation of the breast. Other stimuli which increase circulating prolactin include strong doses of oestrogens, psychic stress, hypoglycaemia, drugs which antagonize dopamine (benzodiazepines, phenothiazines, thioxanthenes, butyrophenones, reserpine, alphanemethyldopa), administration of TRH, and hypothyroidism.

The hypothalamus blocks hypophyseal synthesis of prolactin and produces PIF (prolactin inhibiting factor) which may be identical to dopamine. In some pathological conditions (Chiari–Frommel syndrome, Argonz Del Castillo syndrome, Forbes–Albright syndrome) there is a disturbance of these mechanisms which results in hyperprolactinaemia, galactorrhoea, and amenorrhoea. In such cases, hypothalamic suppression affects both the production of PIF and of LH-RH, thus causing hyperprolactinaemia–hypergonadotrophinaemia. The reaction of the dopaminergic receptors with derivatives of the alkaloids of ergot, in particular 2-bromo- α -ergocryptine, reduces hyperprolactinaemia and galactorrhoea.

The placenta produces the lactogenic hormone, HPL or HCS, which is structurally and immunologically similar to somatotrophic hormone. It is involved in the preparation of the mammary glands, and also has anabolizing, lipolytic, hyperglycaemic, and haemopoietic functions. Prolactin extracted from animal sources is used to stimulate lactation.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of prolactin in pregnancy in laboratory animals.

Somatotrophic hormone (STH) or somatotrophin

(MW 20 000–29 000)

Not contra-indicated in pregnancy.

Somatotrophin is a simple protein, formed from a single chain of 191 amino acids. Growth hormone from other species has a similar structure, but is completely inactive in man. Its biological action is to stimulate the growth of the long bones by stimulating the formation of cartilage, and to produce increase in volume of all major organs, with the exception of the central nervous system. The basis of this growth is a strong anabolic stimulus which is manifested in the retention of certain cellular constituents, such as nitrogen, sodium, potassium, calcium, and chloride, and in the lowering of blood urea levels. The increase

in protein synthesis is accompanied by an increased transformation of lipids into glucides, i.e., the inhibition of lipogenesis and the acceleration of lipolysis (mediated by cyclic AMP), mobilization of fat deposits, and increase in circulating NEFA and hepatic lipids.

Somatotrophin aggravates diabetes, diminishes tolerance to glucose, opposes the action of insulin, and is diabetogenic. Hypoglycaemia increases the production of somatotrophin. The therapeutic use of the hormone is limited to cases of hypophysial insufficiency in the infant.

Somatotrophin does not cross the placental barrier [1, 5, 6].

Administered intravenously to 14 women from 10 to 270 minutes before birth, it did not appear in the foetus [1].

In laboratory animals, somatotrophin caused early and late intra-uterine deaths, as well as prolongation of pregnancy with foetal macrosoma [2, 7, 8, 9, 14, 15, 16]. It has been observed in animals that administration of somatotrophin in pregnancy caused a larger learning capacity in the newborn and a greater alertness in response to conditioned reflexes [11, 12, 13]. In the rat, the hormone administered parenterally from the 7th to the 19th day of pregnancy increased neonatal weight. Some hypertrophy of the neurons was established histologically, and this was accompanied by behavioural changes in the neonates [3]. Later research has demonstrated that somatotrophin cancels the negative effects of starvation on cerebral development [4].

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Thyroid stimulating hormone (TSH) or thyrotropin

(MW 24 000—30 000)

Not contra-indicated in pregnancy.

Thyrotropin is a glycoprotein which contains two sub-units; the alpha unit is identical to that of LH and HCG. The function of thyrotropin is to stimulate

the development of the thyroid (hypertrophy and cellular hyperplasia) and its function of iodine capture, the synthesis and storage of the thyroid hormones, and proteolysis of colloids. These phenomena are mediated by an increase in adenyl cyclase in thyroid cells, and thus of cyclic AMP, which is the intracellular effector of thyrotropin. An analogous action is mediated by prostaglandin E1.

Release of thyrotropin is regulated in the hypophysis by negative feedback by thyroid hormones and iodine. It is stimulated by cold, catecholamines, and serotonin. It is inhibited by antithyroid drugs. The hypothalamus controls the biosynthesis and storage in the hypophysis of thyrotropin by means of the production of TRH (thyroid releasing hormone). This tripeptide (1-pyrroglutamyl-1-histidyl-1-proline amide), has also been obtained by synthesis, and stimulates the formation of cyclic AMP in the hypophysis. Thyrotropin also causes prolactin release.

The placenta produces a thyrotropin practically identical immunologically to that of the hypophysis. The hydatid cyst and the chorionic epithelioma, on the other hand, produce a thyrotropin with a higher molecular weight which does not react immunologically with antihypophysial thyrotropin sera. This 'molar' thyrotropin is able to cause thyrotoxicosis [16,17,18].

Thyrotropic hormone is used exclusively for diagnostic purposes.

Thyrotropin does not cross the placental barrier [1,2,3,4,11,14,15,22]. Some authors have proposed that a slow passage of the hormone occurs towards the end of pregnancy, which is probably related to 'placental senescence' [5]. No embryofoetotoxic or teratogenic effects have been observed.

In the rat and guinea-pig, transplacental passage of thyrotropin is controversial [6,7,8,9,10,19,20,21]. In the rat, the hormone extracted from the homologous hypophysis possessed a weak teratogenic action, while the bovine hormone had marked teratogenic properties [12].

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Clomiphene citrate

Clomid,

2-(*p*-(β -chloro- α phenylstyryl)phenoxy)triethylamine dihydrogen citrate
 (MW 598.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C				

Contra-indicated in pregnancy.

Clomiphene is a racemic compound which can be separated into two isomers. *Cis*-clomiphene is anti-oestrogenic, and *trans*-clomiphene is weakly oestrogenic. *Cis*-clomiphene is five times more active than the racemic compound.

Clomiphene is a derivative of chlorotrianisene, a synthetic non-steroid oestrogen. In experimental animals, it inhibits gonadotrophic function, while in man, it increases production of gonadotrophin. In fact, its slight resemblance to the oestrogens is sufficient to enable it to bind to hypothalamic receptors for oestrogens. The hypothalamus is thus unable to 'measure' oestrogen levels, and secretes 'releasing hormones' into the portal system which stimulate the hypophysis to increase secretion of FSH and LH. In this way, when clomiphene occupies hypothalamic receptors, there is an increase in circulating FSH which initiates the sequence of events leading to ovulation. Clomiphene is used in the treatment of anovulatory sterility and of oligospermia, and also as a diagnostic test (the clomiphene test).

The wide use of clomiphene to induce ovulation has led to contradictory conclusions on possible teratogenic effects arising during pregnancy following therapy [15,16]. It has not been ascertained with certainty that clomiphene is teratogenic in humans, and the incidence of perinatal mortality, and postnatal behaviour, are normal [1, 2, 3, 4, 5, 12, 13]. A retrospective study on the results of therapy with clomiphene citrate in 2616 women with sterility arising from anovulatory cycles showed 2196 pregnancies. Of these, 1744 went to term, 45 were interrupted before term, there were 407 spontaneous abortions and intra-uterine deaths, 136 multiple pregnancies, and 38 cases of foetal malformations. The authors conclude that clomiphene citrate does not have teratogenic

effects in pregnancy occurring after therapy with the drug. It is, however, contra-indicated in established pregnancy [1].

Other workers reached the same conclusion. In 160 pregnancies which occurred after treatment with clomiphene, there was a 12.3% incidence of multiple pregnancies and a 10.8% incidence of spontaneous abortions. There was no increase in congenital malformations [2]. In 140 pregnancies in 163 women treated with clomiphene for sterility, there were 90 spontaneous deliveries at term, 19 premature births, 4 immature births, 27 spontaneous abortions, and 12 twin pregnancies [3]. In 225 pregnancies following clomiphene treatment, the frequency of multiple births was 13%. Two neonates were born with malformations (Down's syndrome and anal imperforation). The incidence of malformations was no greater than that in controls [4]. One case of multiple malformations was described in the infant of a mother who had taken clomiphene for two cycles before conception. However, she had also been treated with dimenhydrinate for hyperemesis during the first trimester [5]. In another retrospective study on 96 pregnancies in 86 women treated with clomiphene for sterility, it was seen that the percentage of malformations was not different from average [12].

The effects following on the administration of clomiphene during pregnancy are extremely controversial and only rarely mentioned in the literature. While some authors refer to teratogenic effects [6], which are represented specifically by arterial and venous fistulae, others [8] do not report any foetal damage after the drug or during the first trimester. However, there are no therapeutic indications for the use of clomiphene in pregnancy, and the cases mentioned in the literature almost always refer to unrecognized pregnancies. Should this occur, there are no indications, in our opinion, for interruption of pregnancy.

In the rat, mouse, and rabbit, clomiphene was embryofoetotoxic and teratogenic [6,7,8,9,10,11,14]. In the rat, oral doses of 8 mg/kg during the period of organogenesis gave rise to teratogenic effects. Larger doses, 40–200 mg/kg, were only embryofoetotoxic [6]. Subcutaneous administration of clomiphene on the 12th day of pregnancy caused teratogenic effects which increased at higher doses [6]. Subcutaneous doses of 3 mg/kg on the 5th, 7th, and 9th days of pregnancy caused inhibition of placental development. At the same dose, on the 12th, 14th, 16th, and 18th days of pregnancy, clomiphene led to foetal death or resorption [10].

In the mouse, doses of 0.1–10 mg/kg at various stages of pregnancy were embryofoetotoxic [8]. In the rabbit, oral doses of 20–40 mg/kg from the 8th to the 15th day of gestation gave rise to teratogenic effects [6]. Administration of clomiphene to the rabbit during the first period of pregnancy caused gastro-schisis, cranioschisis, cleft palate, and hydrocephalus [7]. Intramuscular doses of 25 μ g on the 10th–12th days of pregnancy were foetotoxic [9].

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Cyclofenil

4,4-(cyclohexylidene-methyl)bis-phenylacetate (MW 364.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C				

Contra-indicated in pregnancy.

Cyclofenil acts in a similar way to clomiphene by occupying hypothalamic oestrogen receptors, thus lifting the inhibition exerted by these receptors on 'releasing hormones'. Cyclofenil is used in the therapy of sterility, to induce ovulation. Compared to clomiphene, it has fewer side effects and causes fewer multiple pregnancies. It can cause galactorrhoea.

In pregnancies following cyclofenil, an increased incidence of spontaneous abortion and premature birth has been noted [5]. In 88 pregnancies, induced after stimulation of ovulation with cyclophenile, 26 ended in spontaneous abortion or premature birth [5]. Although there have been no reports of harmful effects on the foetus, the possibility of pregnancy should be excluded before commencing cyclofenil treatment [2]. Cyclofenil has no therapeutic role in pregnancy.

In the mouse, doses of 20 mg/kg from the 1st to the 5th day of pregnancy or from the 1st to the 9th day of pregnancy caused interruption of the pregnancy in 100% of cases [1]. Administered half way through pregnancy, cyclofenil resulted in the death of the embryo [3].

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Para-oxypropiofenone or paraoxyphone

p-hydroxy-propiofenone (MW 150.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P				

To be used with care in pregnancy.

Para-oxypropiofenone is an inhibitor of gonadotrophic (particularly LH) and of thyrotrophic hormones. It has been used in the treatment of hypophysial hyperactivity, of chorionic epithelioma, and of Basedow's disease.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy. Some authors have used the drug in the treatment of 'hyper-hormonal pregnancy', obtaining a reduction in pregnandioluria, and regularizing the development of the pregnancy and the birth without foetal side effects [1]. We do not think that para-oxypropiofenone has any therapeutic indications in pregnancy, and we advise against its use.

In the mouse, rat, rabbit, and guinea-pig, para-oxypropiofenone was embryotoxic if administered in the early part of pregnancy [3, 4, 5, 6].

In the mouse, oral doses of 500 mg/kg during the 2nd week of gestation did not affect the development of the pregnancy, birth, or lactation [2]. A subcutaneous dose of 500 mg/kg in the 1st week of pregnancy resulted in an increase percentage of foetal resorptions, which was not observed if administration took place during the 2nd and 3rd weeks of pregnancy [3].

In the guinea-pig, subcutaneous doses of 150 mg/kg in the second half of pregnancy resulted in a high frequency of spontaneous abortion [3].

In the rat, subcutaneous doses of 150 mg/kg for 3 months (before and during eventual pregnancy) caused sterility (often in animals treated in the pre-pubertal period), but if pregnancy occurred, this developed normally, even with continued treatment. Parturition occurred at the normal time, the offspring all survived, and lactation and postnatal development were normal [4].

In the rabbit, doses of 100 mg/kg for 10 days in the first phase of pregnancy did not affect the development of pregnancy. Doses of 200 mg/kg in the second half were not embryofoetotoxic or teratogenic. Doses of 500 mg/kg in the second half of pregnancy almost always resulted in abortion, apparently because of toxicity [5]. Para-oxypropiofenone was administered at doses of 100 mg/kg

either intramuscularly or intravenously on the 5th, 10th, 13th, 16th, 18th, and 20th days of pregnancy. This caused foetal death and resorption only in those cases treated in the first half of pregnancy, while in those treated in the second half, the pregnancy developed normally [6].

Para-oxypropiofenone reduced excretion in the urine of 17-ketosteroids [6].

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3. THYROID AND ANTITHYROID DRUGS

In addition to the natural hormones (T3 and T4) there are drugs available, based on bromides, which have a competitive action or which reduce iodine capture and biosynthesis in the thyroid (thiouracil and imidazole drugs). Calcitonin, a regulator of bone metabolism, has recently been introduced. The following drugs are described here:

	Recommendation	Page
Iodothyroglobulin	NC	152
Tri-iodothyronine	NC	152
Thyroxine	NC	152
Di-iodotyrosine	NC	152
Dextrothyroxine sodium	NC	155
Bromo-iodocasein	P (C during lactation)	155
Dibromotyrosine	P	156
Carbimazole	C	157
Methimazole	C	158
Aminometrazole	C	160
Propyl-thiouracil	P (C during lactation)	160
Methyl-thiouracil	P (C during lactation)	160
Calcitonin	C	162

During pregnancy, administration of thyroid hormone is not contra-indicated, when there are therapeutic indications. However, the use of antithyroid drugs and calcitonin is not advised.

Iodothyroglobulin

Tri-iodothyronine or liothyronin or T3

(MW 673.0)

Thyroxine or dried thyroid or T4

(MW 888.9)

Di-iodotyrosine or DIT

(MW 433.0)

None of the above is contra-indicated in pregnancy.

Hormonal activity of the thyroid is related principally to two substances: thyroxine (T4) and tri-iodothyronine (T3), iodinated amino acids which are incorporated into the glycoprotein thyroglobulin in the thyroid. Iodine is

captured by the thyroid and serves to iodinate the amino acid tyrosine to mono-iodo-tyrosine (MIT), and di-iodo tyrosine (DIT), the precursors of T3 and T4. These hormones are released into the circulation by proteolysis of thyroglobulin. Thyroid hormones accelerate metabolism, increasing oxygen consumption, excretion of nitrogen, calcium, and water, and diminish body weight. Therapy with thyroid hormones is indicated in hypothyroidism, which is associated with obesity.

Dried extract of thyroid is used therapeutically in addition to the pure hormones thyroxine and tri-iodothyronine. The hypocholesterolaemic action of the thyroid hormones is present also in the dextrorotatory stereo-isomers, but there is a smaller effect on basal metabolism. Dextro-thyroxine sodium is used in the treatment of angina of effort. Di-iodotyrosine (DIT) has the same actions as thyroid extract, since this activity depends only on the iodine content. It represents the only source of this element. Tri-iodothyronine is one of the two thyroid hormones. It is believed that thyroxine acts only after having been transformed into tri-iodothyronine, which has a more intense and rapid effect. Thyroglobulin is an extract of porcine thyroid, and contains more than 0.7% of organic iodine. Thyroxine is the second thyroid hormone, and has a delayed and cumulative effect.

The thyroid hormones slowly cross the placental barrier but only in small quantities [1, 2, 3, 11, 12, 13, 14, 19, 21, 51]. Administration of the thyroid hormones is quite safe in pregnancy, and is advised in cases of maternal hypothyroidism [4, 10, 15, 17, 22, 46, 47, 48]. There are many indications of increased perinatal mortality and congenital malformations in the infants of hypothyroid mothers who were not treated [4, 5, 6, 7, 8, 10, 16, 18, 19, 20]. When tri-iodothyronine is administered in pregnancy, it often depresses the concentration of thyroid hormones in foetal blood [19]. Conversely, thyroxine crosses the placental barrier more slowly, and in amounts insufficient to affect the foetal thyroid [45]. Recently, the intra-amniotic administration of thyroxine (200 μ g) has been described in the treatment of foetal pulmonary immaturity [49].

Thyroxine passes into breast milk [50].

In the guinea-pig, rat, and rabbit, transplacental passage of the thyroid hormones has been shown [23, 24, 25, 26, 27, 28, 29, 30, 44]. Thyroid administered to the guinea-pig at doses of 0.1–0.15 mg every 4 days subcutaneously crossed the placental barrier [23]. In the rabbit, labelled thyroxine administered intravenously was found in foetal serum within a few hours [30].

The effects of administration of thyroid hormones in pregnancy in the mouse, rat, rabbit, and hamster are controversial [31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43]. In the mouse, thyroxine administered in varying doses and at different stages of pregnancy caused the appearance of cataracts in 38% of neonates [35, 36]. However, the same authors, in successive studies [37], demonstrated that genetic factors also play a considerable role in the aetiology of these malformations. The frequency of malformations varied between 20% in

the Wistar strain to 2.1% in Aec Commentry strain and 1.7% in Norwegian Piebald strain.

In the rabbit, thyroid hormone administered at high doses caused an increase in foetal resorptions [39], but was not teratogenic [40]. In chick embryo, neither thyroxine nor tri-iodothyronine was teratogenic at doses of 3–24 µg per egg, given on the 2nd, 3rd, or 5th day of incubation [41].

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Dextrothyroxine sodium

sodium salt of

D- β -((3,5-di-iodo-4-hydroxyphenoxy)-3,5-di-iodophenyl)-alanine
(MW 798.9)

Not contra-indicated in pregnancy.

Dextrothyroxine lowers cholesterol levels and beta-lipoproteins, while only slightly affecting pre-beta-lipoprotein and basal metabolism. The thyroid hormones in general increase hepatic biosynthesis of cholesterol, but they increase further metabolism of bile acids, and thus promote their elimination in faeces. Dextrothyroxine is contra-indicated in patients who have coronary disease, are diabetic, have liver disease, or are on anticoagulant therapy.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rabbit, oral administration of dextrothyroxine at doses of 2 mg/day in the first 15 days of pregnancy caused an increase of more than 20% in embryonal mortality. Administered in the last 15 days of pregnancy, however, the drug did not cause a significant increase in foetal mortality, although it produced an increase in organ weights in the absence of histopathological changes [1].

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Bromo-iodocaseine

(MW ~25 000)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					C
Chronic	P	P	P		C

To be used with care in pregnancy, and is contra-indicated during lactation.

Bromo-iodocaseine represents a way of administering two halogens which are released from the protein during digestion, and act synergistically in inhibiting hypophysial thyrotropic hormone storage, while competing for capture by the thyroid.

Bromo-iodocaseine should be used with care in pregnancy. If it is true that during pregnancy there is an increased metabolic requirement for iodine, both in normal and hypothyroid women, it is also true that any iodine administered crosses the placental barrier rapidly [1, 2, 3, 4, 5, 6, 7, 8, 9, 20, 23], and may cause possible neonatal goitre if it accumulates in the foetus. This leads to difficulty in breathing and thyroid disturbances which may even give rise to cretinism [1, 2, 6, 10, 11, 12, 13, 14, 15, 16, 17, 20, 21, 22, 23, 24].

Bromo-iodocaseine passes into breast milk, for which reason suckling during therapy is contra-indicated [18, 19, 20].

No experimental studies have been found on the use of bromo-iodocaseine in pregnancy in laboratory animals.

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Dibromotyrosine

(MW 338.98)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Dibromotyrosine is an antithyroid drug which makes use of the competitive effect of bromine on iodine capture, and inhibits storage of hypophyseal thyrotropic hormone, as does iodine.

Dibromotyrosine has been used in the treatment of hypothyroidism throughout pregnancy with doses of up to 1.2 g/day, without causing any side effects in the foetus [1]. Despite this, we advise that dibromotyrosine should be used with caution in pregnancy.

In the rat, dibromotyrosine administered at doses above therapeutic was neither embryofoetotoxic nor teratogenic [2].

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Carbimazole

Neo-Mercazole, 2-carbethoxy-thio-1-methylglyoxaline (MW 186.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		C

Contra-indicated in pregnancy and during lactation.

The drugs used in the treatment of hyperthyroidism are derivatives of thiocarbamide. These include thiouracil and imidazole derivatives. They reduce iodine capture and interfere with synthesis of thyroxine and tri-iodothyronine, blocking the oxidation of iodine by inhibiting the peroxidase enzyme implicated in the synthesis of iodotyrosine, and in the coupling of iodotyrosine, to form iodothyronine. Carbimazole, an imidazole derivative, reduces the formation of di-iodotyrosine and increases that of thyroxine. It is rapidly absorbed in the digestive tract and equally rapidly eliminated in the urine.

All the antithyroid drugs cross the placental barrier and are found in maternal milk. This being so, carbimazole and similar drugs alter the development and function of the foetal thyroid-hypophyseal axis. The goitre which can be produced rapidly regresses, however [1]. Carbimazole interferes with

development of the foetal thyroid if administered from the 14th week of pregnancy onward [2,3,4]. Simultaneous administration of thyroid hormone to the mother appears to minimize this risk [5]. Administration of carbimazole to two hyperthyroid patients at doses varying between 15 and 40 mg/day throughout pregnancy produced hypothyroidism in the neonates [6]. Administration of carbimazole in the first trimester may be teratogenic [7]. In 25 hyperthyroid patients at doses of 30 mg/day during the first and second trimesters, the drug caused the birth of two malformed infants, one with adactyly and the other with bilateral congenital cataracts [7].

Carbimazole passes into breast milk, and can produce goitre in the suckling [8].

No experimental studies have been described on the use of carbimazole in pregnancy in laboratory animals.

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Methimazole

2-mercapto-1-methyl-imidazole (MW 114.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		C

Contra-indicated during pregnancy and lactation.

Methimazole is an antithyroid drug with an imidazole structure, very similar to carbimazole (see page 157).

Methimazole crosses the placental barrier [6,7,13,21,23]. Administration of methimazole and its derivatives is contra-indicated throughout pregnancy because, in addition to its greater inducing effects which are linked to its mechanism of action, and which are expressed in the foetus, it can cause teratogenic effects, particularly if administered in the first months of pregnancy [1,2,3,

4, 5, 6, 9, 10, 11, 13, 14, 15, 16, 17, 25, 28]. Of four neonates from two patients who had taken methimazole and propylthiouracil in pregnancy, two presented with neonatal goitre [1]. In 12 cases, therapy with thiouracil or with methimazole during pregnancy was related to congenital goitre in the neonates, which lasted for many months after birth [24]. The case has been described of a neonate affected with microsomia and club foot, born to a patient who had taken methimazole at various stages of pregnancy [2]. Two patients who had taken the drug in pregnancy gave birth to infants with defects of bone structure and of the cranium [3]. One mother treated throughout pregnancy with methimazole gave birth to an infant with severe hypothyroidism [5]. There are references in the literature to the administration of methimazole at low doses for limited periods without foetal side effects [8, 12, 18, 19, 20, 21].

Methimazole passes into breast milk, and can cause goitre in the infant [27].

In the rabbit, methimazole administered for 21 days of pregnancy was neither embryofetotoxic nor teratogenic, but it did affect postnatal growth [22].

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Aminometrazole

2-amino-4-methylthiazole bitartrate (MW 264.26)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		C

Contra-indicated in pregnancy and lactation.

Aminometrazole is an imidazole derivative with antithyroid action (see carbimazole, page 157).

Administration of aminometrazole in pregnancy is contra-indicated for the same reasons as given for metimazole (see page 158).

No experimental studies have been described on the use of aminometrazole in pregnancy in laboratory animals.

Propyl-thiouracil

3,4-dihydro-2-mercapto-6-propylpyrimidin-4-one (MW 170.2)

Methyl-thiouracil

3,4-dihydro-2-mercapto-6-methylpyrimidin-4-one (MW 142.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		C

Both compounds should be used with care in pregnancy, and are contra-indicated during lactation.

Propyl- and methyl-thiouracil are more rapidly absorbed and eliminated than the imidazoles. In addition, they have a shorter biological half life. For further information, see carbimazole (page 157).

Propyl-thiouracil crosses the placental barrier [1, 2, 3, 4, 5, 6, 7, 8, 9, 25, 38, 54, 55]. It should be used with extreme care after the third month of pregnancy and particularly in the last trimester, since it can provoke goitre and hypothyroidism in the foetus by inhibition of the foetal thyroid and consequent stimulation of thyrotropin [3, 6, 9, 10, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 25, 28, 36, 37, 38, 48]. It has been calculated that 50% of cases of congenital goitre are due to therapy with propyl-thiouracil or iodides [47].

There have also been reports of hyperthyroid patients being treated in pregnancy with thiouracil, either alone or in combination with surgery or with

thyroid hormones, with no effect on the foetal thyroid. For this reason, many authors maintain that propyl-thiouracil is the safest of the antithyroid drugs, especially if administered with continuous monitoring at doses of 150 mg/day or less, and suspended at term [1, 5, 11, 12, 24, 26, 27, 29, 30, 31, 32, 46, 49, 51, 52, 53, 54, 55].

Two patients treated with 200 mg thiouracil throughout pregnancy for thyrotoxicosis produced one healthy infant and one with an enlarged thyroid [12]. A patient who had received 200 mg thiouracil on alternate days died 6 months into the pregnancy. The foetus had a hyperplastic thyroid [13]. In 60 patients treated with thiouracil in pregnancy, 15 infants had enlarged thyroids and/or cretinism. The remainder were normal [14]. Twins with goitre were born to two patients who had taken thiouracil in pregnancy [16]. A study on 41 pregnancies in 30 patients who had taken thiouracil showed that five infants had goitre and in five cases the foetus died [23]. A successive study by the same authors demonstrated that the intelligence quotient of 37 babies, including three cases of congenital goitre, who had been exposed to thiouracil during foetal life were the same as controls [24]. In a study on 132 pregnant women treated with thiouracil, it was observed that 21 neonates presented with enlarged thyroids (3 died as a result of tracheal compression, 7 died immediately after birth), 5 patients had spontaneous abortions, and 6 gave birth prematurely [20]. Other studies showed the birth of normal infants to patients treated with propyl-thiouracil at various stages of pregnancy. These studies included respectively 8 [30], 22 [32], 14 [51], 17 [52], and 4 [53] pregnant women. In the last two studies, the doses were 50–300 mg/day [52] and 50–400 mg/day [53].

The thiouracils pass into breast milk, and therefore are contra-indicated during lactation, because of possible effects on the infant thyroid gland [1, 33, 35, 50].

In the mouse, rat, guinea-pig, and rabbit, thiouracil caused an increase in weight of the foetal thyroid and a retardation of cerebral development, but there were no malformation [39, 40, 41, 42, 43, 44, 45].

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Calcitonin

Calcitare (MW 3600)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Calcitonin is a polypeptide containing 32 amino acids, and produced by the 'C' cells of the thyroid, the parathyroid, and the thymus, all embryologically derived from the ultimate brachial body. Calcitonin, together with parathormone and vitamin D, is one of the regulators of metabolism of calcium and of phosphate. If calcaemia is increased, it can reduce bone resorption by the osteoclasts. If calcaemia is reduced, parathormone is secreted, which increases bone resorption, reduces urinary calcium excretion, and promotes greater intestinal absorption of calcium. Calcitonin induces inactivation of vitamin D₃ and 1,25 dihydroxy-D₃ and thus, indirectly, intestinal absorption of calcium (see vitamin D, page 266).

In the kidneys, calcitonin, in addition to producing vasodilation, also increases elimination of phosphates, sodium, potassium, magnesium, and water by blocking tubular reabsorption and reduces elimination of hydroxyproline, which is derived from proline, and is involved in the biosynthesis of a polypeptide precursor of collagen.

At the cellular level calcitonin reduces active transport of calcium out of the cells by blocking the so-called calcium pump. In addition, it reduces the concentration of free calcium in the cytoplasm which is actively accumulated in the mitochondria and in the endoplasmic reticulum (first step in calcification). Conversely, parathormone increases passive entry of calcium into the cells and activates adenyl cyclase which produces an increase in cyclic AMP. Calcium is released from the mitochondria and is transferred in the free form into the cytoplasm.

Calcitonin reduces insulin production and thus tolerance to glucose. It also has an anti-inflammatory action, due to its inhibition of prostaglandin synthesis.

Biosynthesis and storage of calcitonin are stimulated by hypercalcaemia, adrenaline, serotonin, histamine, glucagon, prostaglandin E₁, gastrin, and cholecystokinin. The effect of the latter is important in the postprandial regulation of calcaemia. The oestrogens at high doses can increase production of calcitonin, and reduce that of parathormone.

Calcitonin is used in the treatment of thyrotoxic hypercalcaemia and of those diseases characterized by increased bone resorption (osteoporosis, Paget's disease).

During pregnancy, blood levels of calcitonin are increased. In cord blood, the concentration is higher than that of maternal blood. This increase persists during the neonatal period and is probably related to foeto-neonatal thyroid activity [1, 2, 3, 4]. The effects of administration of calcitonin during pregnancy are not known, nor is there information on its transplacental passage. However, changes in calcium metabolism can produce cardiovascular malformations in the foetus.

In the rat, doses of 5–20–80 IU/kg/day administered subcutaneously from the 6th to the 15th day of pregnancy were not embryofetotoxic. The

appearance of skeletal malformations at higher doses was not attributed to drug treatment. Administered in the same way, from the 15th day of pregnancy, calcitonin at higher doses caused a reduction in foetal weight at birth, and an increased incidence of intra-uterine deaths [5]. At doses of 86 IU/kg/day, calcitonin reduced the weight gain of pregnant animals, and caused death in about 50% of cases. At autopsy, conspicuous dilatation of the renal tubules was observed [5].

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4. INSULIN, GLUCAGON, AND ORAL ANTIDIABETIC DRUGS

Insulin and glucagon are among the most important regulators of glucose metabolism. The sulphonylureas and the biguanides are used in the treatment of diabetes, and they are able to stimulate storage and utilization of insulin and modify the metabolism of glucose, reducing its formation and increasing its utilization. Diazoxide has the opposite effect. The following drugs are discussed in this chapter:

	Recommendation	Page
Insulin	NC	166
Glucagon	NC	168
Carbutamide	C	169
Tolbutamide	C	170
Chlorpropamide	C	172
Acetohexamide	C	174
Glipizide	C	174
Glibenclamide	C	175
Tolazamide	C	176
Glicyclamide	C	177
Gliclazide	\bar{C}	177
Phenformin	C	178
Metformin	C	179
Diazoxide	P	179

During pregnancy, the use of insulin is not contra-indicated and is the only suitable treatment for diabetes in this situation. Insulin does not cross the placental barrier, and by correcting maternal glucose metabolism it eliminates any risk of teratogenesis. The sulphonylureas are contra-indicated in pregnancy because they cross the placental barrier and so stimulate foetal production of insulin. Foetal hyperinsulinaemia is dangerous at birth and diminishes production of pulmonary surfactant during the last phase of pregnancy. It thus aggravates the pulmonary immaturity characteristic of the foetus of a diabetic mother. There is some doubt regarding teratogenic effects with the sulphonylureas. The biguanides are contra-indicated because of poor control of glycid metabolism during pregnancy. Diazoxide is also contra-indicated, since it has few therapeutic applications.

Insulin

(MW ~6000)

Not contra-indicated in pregnancy.

Insulin is composed of two chains of amino acids linked by two disulphide bridges. It has been produced by synthesis, but, commercially, methods of extraction from natural sources are used. Insulin is produced by the beta cells of the pancreas, starting from pro-insulin. Insulin regulates the use of glucose by controlling its entry into cells, directly stimulates the synthesis of glycogen and of proteins, and indirectly stimulates synthesis of fatty acids. It inhibits the action of cyclic AMP without necessarily lowering its concentration, and thus blocks glycogenolysis and lipolysis. It also blocks proteolysis, probably because it renders the lysosomes more stable.

According to several authors, insulin does not cross the placental barrier [1, 34, 36, 45]. Other authors [2], without producing any evidence, claim the opposite. Still others recognize its passage, but claim that a large part of the hormone is degraded [3]. At therapeutic doses, however, insulin is harmless in pregnancy, both to the mother and to the foetus [26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 46, 47, 48, 49, 50, 51]. Only insulin shock repeated several times during the first trimester of pregnancy has been shown to cause spontaneous abortion in a number of cases. It also causes intra-uterine death of the foetus, mental deficiency, blindness, and cranial deformities. These effects may be due to hypoxia, and not to insulin itself [4, 5, 6, 7].

Administration of insulin at various stages of pregnancy is neither embryo-foetotoxic nor teratogenic, and in fact improves foetal and neonatal prognosis. This was observed in 28 patients between 19 and 42 years old who were treated with 10–15 IU/day [26], in 84 patients [28], in 64 patients treated with 50 IU/day [37], in 73 patients [38], in 28 patients with latent diabetes treated with 10–15 IU/day [48], and in numerous other cases treated with 16–200 IU/day [49].

In the rat, mouse, rabbit, and chick embryo, insulin was embryofoetotoxic and teratogenic [4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 22, 23, 24, 25, 41, 42, 43, 44]. In the rat, subcutaneous doses of 7–8 IU throughout pregnancy caused an increase in foetal resorptions, reduction of weight gain, and malformations of the limbs [15]. A subcutaneous dose of 1 IU from the 18th to the 20th and from the 19th to the 21st days of pregnancy caused malformations of the limbs and excessive weight gain, with a relative increase in lipids [17].

In the mouse, intraperitoneal doses of 0.1 IU on the 9th day of pregnancy caused changes in the central nervous system (exencephaly and anencephaly), and malformations of the digestive tract (umbilical hernia, gastroschisis) [19, 20].

In the rabbit, doses of 20–22 IU from the 6th to the 7th and from the 9th to the 10th days of pregnancy caused an increase in foetal resorptions, and

malformations of the central nervous system, the cardiovascular system, and the skeleton [22, 23]. Intravenous doses of 20–22 IU from the 6th to the 11th day of pregnancy caused an increase in foetal resorptions, spina bifida, deformities of the limbs, cleft palate, and malformations of the eye [24].

In chick embryo, injection into the yolk of 2 IU insulin after 24 and 120 hours of incubation caused micromelia and other skeletal deformities [25].

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Glucagon

(MW 3484.76)

Not contra-indicated in pregnancy.

Glucagon is a polypeptide of 29 amino acids, and is synthesized in the alpha cells of the pancreas. Administration of this hormone causes a significant increase in glycaemia as a result of stimulation of hepatic glycogenolysis, by means of increased synthesis of AMP which, in turn, activates phosphorylase, an enzyme which catalyses the hydrolysis of glycogen to glucose. Glucagon is almost exclusively used in the therapy of hypoglycaemia.

Glucagon does not cross the placental barrier [9]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

In the rat, glucagon has a teratogenic effect, but it has no harmful effects on the foetus in the rabbit [6, 8]. In the rat, doses of 20–200 $\mu\text{g}/\text{day}$ caused cataracts in the foetus [5]. At doses of 300 $\mu\text{g}/\text{day}$ on the 7th, 8th, and 9th days of pregnancy, it provoked glaucoma in the foetus. At doses greater than 400–500 $\mu\text{g}/\text{day}$, it caused microphthalmia and skeletal malformations [6]. In the rabbit, intravenous doses of 100 μg from the 10th day until term had no teratogenic effects. The only finding of note was the early appearance of the nuclei of epiphyseal ossification [8].

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Carbutamide

N1-sulphonyl-N 2-n-butylurea (MW 271.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Carbutamide is an oral antidiabetic derivative of sulphonylurea. Its action is the result of: (1) increase in insulin production by the pancreas (as is seen in insulinaemia in the pancreatic: duodenal vein, together with parallel diminution in the granules of β islet cells); (2) release of inactive insulin bound to globulins (more than 50% of insulin is normally in the bound form).

The therapeutic use of carbutamide, as with all oral hypoglycaemics, is contra-indicated in pregnancy because of the embryofoetotoxic and teratogenic effects produced by its administration [2, 3, 4, 5, 6, 7, 24, 28]. Although other authors stress that these effects cannot be related with certainty to the use of carbutamide in pregnancy (since the incidence of malformations in the infants of diabetic mothers is higher than in control groups anyway), they maintain that it is preferable not to use the drug in pregnancy, but to rely on using insulin where necessary [8, 9, 10, 11, 23, 26, 29]. Two cases of neonatal malformations have been described (one with Pierre-Robin syndrome and club foot, the other with microcephaly) which were attributed to the use of carbutamide in pregnancy [4]. In ten diabetics treated in pregnancy with carbutamide, two neonates had cardiac malformations, and there was one case of intra-uterine death [5]. Another instance of intra-uterine death was described during the course of therapy with carbutamide in the 8th month of pregnancy, and there was a further case of foetal death with polyhydramnios following treatment throughout pregnancy [6]. On the other hand, one pregnancy has been described where the mother was treated with carbutamide with no harmful effects on the foetus [12], and another three diabetic women treated with the drug in pregnancy gave birth to normal infants [13, 14]. In four cases, carbutamide was used at various stages of pregnancy. Three infants were completely unaffected, and there was one intra-uterine death [9].

In the mouse, rat, and rabbit, carbutamide was embryofoetotoxic and teratogenic [6, 15, 16, 17, 18, 19, 20, 21, 22, 25, 27]. In the rat, oral doses of 150–350 mg/day from the 1st to the 12th day of pregnancy were embryo-foetotoxic (foetal mortality) and teratogenic (microphthalmia) [15, 16, 17]. An oral dose of 500 mg for 3 days from the 8th to the 14th day of pregnancy was foetotoxic and teratogenic, causing cleft palate and malformations of the urogenital tract [18]. A single dose of 1–2 g/kg from the 7th to the 13th

day of pregnancy was teratogenic (microphthalmia) [19]. Administration of the drug at varying doses caused an increase in foetal resorptions, teratogenic effects, and in 95% of cases gave rise to atrophy of the optic nerve, homophthalmia, microphthalmia, and exencephaly and spina bifida [6]. At doses of 132–1200 mg/kg a single dose from the 7th to the 14th day was foetotoxic (intra-uterine death) and teratogenic (malformations of limbs and tail) [20].

In the mouse, oral doses of 800 mg/kg/day from the 1st to the 12th day of pregnancy were lethal or teratogenic, causing malformations of the limbs and cleft palate [21].

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Tolbutamide

Pramidex, Rastinon,

N-(4-methylbenzenesulphonyl)-*N'*-*n*-butylurea (MW 270.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Tolbutamide is a sulphonylurea with hypoglycaemic action mediated by increased liberation of insulin in the pancreas. It also modifies metabolism of cyclic AMP in various tissues.

Tolbutamide crosses the placental barrier [1, 37, 42]. It is present in the blood of the neonates for many hours after birth [30]. Tolbutamide is embryo-foetotoxic and teratogenic [2, 3, 4, 5, 6, 7, 8, 10, 11, 35, 42, 43, 44, 46]. One case has been described of a premature infant of a mother treated with tolbutamide at a dose of 0.5 g/day throughout pregnancy, who had syndactyly, hydrocephalus, dextrocardia, and malformations of the ear [8]. Another infant has been described with syndactyly as a possible consequence of treatment of the mother with tolbutamide in pregnancy [10]. Thrombocytopenia, polydactyly, and anomalies of the ears have also been described in the infant of a mother taking 250 mg/day throughout pregnancy [11], and Fallot's tetralogy in the offspring of a mother treated with 1 g/day throughout pregnancy [35]. Other authors believe that the use of tolbutamide in pregnancy is relatively safe, compared to other sulphonylureas, after the first trimester [12, 13, 14, 15, 16, 17, 25, 26, 27, 34, 35, 36, 37, 38, 39, 40, 41, 47]. Eight diabetic women treated with tolbutamide gave birth to normal infants [18]. Three further cases have been described of women treated with tolbutamide during pregnancy who had normal infants [15, 17].

Tolbutamide passes into breast milk [45].

In the rat, mouse, and rabbit, administration of the drug in pregnancy gave conflicting results. Some authors refer to the appearance of embryofoetotoxic and teratogenic effects [19, 20, 21, 22, 28, 29, 31, 32, 33], but others reported no such side effects [23, 24, 25]. In the rat, a single oral dose of 200 mg/day from the 1st to the 12th day of pregnancy was foetotoxic and teratogenic [19]. A parenteral dose of 12.5–125 mg/kg from the 1st to the 20th day of pregnancy was embryofoetotoxic but not teratogenic [20]. An oral dose of 300 mg/kg throughout pregnancy was foetotoxic [21].

In the mouse, a subcutaneous dose of 1 g was teratogenic, causing changes in the central nervous system [22]. An oral dose of 100 mg/kg throughout pregnancy was not embryofoetotoxic or teratogenic [23].

In the rabbit, an intramuscular or subcutaneous dose of 250 mg/kg from the 7th day until the end of pregnancy was not embryofoetotoxic or teratogenic [24].

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Chlorpropamide

Diabinese, Melitase,

1-(p-chlorobenzenesulphonyl)-3-propylurea (MW 276.7)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Chlorpropamide is an orally active antidiabetic, analogous to carbutamide (see page 169), but differing from the latter in that it is more slowly metabolized and because its therapeutic margin is narrower.

Chlorpropamide crosses the placental barrier [14]. When used in pregnancy, it causes embryofoetotoxic and teratogenic effects, and an increase in perinatal mortality [1, 2, 3, 4, 5, 8, 15, 16, 17, 19, 20, 23, 24, 25]. Various authors believe that the use of chlorpropamide in pregnancy produces no side effects in the mother or the foetus [7, 8, 14, 21, 26]. A diabetic mother treated with 500 mg/day throughout pregnancy gave birth to an infant with syndactyly, hydrocephalus, and malformations of the ear and the heart [5]. In 50 diabetic pregnant women treated with chlorpropamide, there were two neonatal deaths, one as a result of prematurity and the other because of diaphragmatic hernia. Despite this, the authors believe that the drug may be used in pregnancy at doses of 100 mg/day without risk to the foetus [7]. Other workers [8] refer to serious hypoglycaemia in an infant whose mother had taken chlorpropamide in pregnancy at doses of 500 mg/day until parturition. A transfusion was necessary, and the infant was judged normal only at one year of age. Other studies have not reported malformations in 34 offspring of patients treated with chlorpropamide in pregnancy [9]. At doses of 500 mg/day, the drug caused increased perinatal mortality, which was particularly noticeable in the infants of mothers over 35 years old [4].

In the rat, chlorpropamide had no teratogenic effects, but was embryo-foetotoxic [10, 11, 12, 13]. Oral doses of 200–300 mg/day from the 1st to the 12th day of pregnancy caused a significant increase in foetal resorptions [13]. The same dose given orally from the 11th to the 12th day of pregnancy caused a 20% incidence of abortions [12].

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Acetohexamide

Dimelor (MW 324.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Acetohexamide is a sulphonylurea with a hypoglycaemic action similar to that of carbutamide (see page 169). Acetohexamide is metabolized to hydroxyhexamide, which also has hypoglycaemic activity, and which has a plasma half life of 6 hours.

Acetohexamide is contra-indicated in pregnancy, as are other sulphonylureas, although for this drug there are no specific references in the literature, only the advice of the manufacturers [1].

In laboratory animals treated for two generations, acetohexamide was not teratogenic [1].

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Glipizide or glidiazineamide

Glibenese, Minodiab,

N-(4-(β -(5-methylpyrazin-2-carboxyamido)-ethyl)-benzene sulphonyl)-*N'*-cyclohexylurea (MW 445.53)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Like the other sulphonylureas (see carbutamide, tolbutamide, etc.), glipizide has a hypoglycaemic action, and probably acts only in the presence of residual endogenous insulin production. It is rapidly absorbed and equally rapidly eliminated, without showing signs of accumulation.

Glipizide is contra-indicated in pregnancy, as are other sulphonylureas, although there are references to its lack of foetal toxicity. Four diabetic patients were treated with the drug from the 32nd week of pregnancy onwards, at doses varying between 2–10 mg/day, without harmful effects in the mother or the foetus [1].

In the mouse, glipizide slowly crossed the placental barrier in small quantities [2].

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Glibenclamide

Euglucon, Semi-Daonil, Daonil,

N-4-(2-(5-chloro-2-methoxybenzamido)-ethyl)phenylsulphonyl-*N'*-cyclohexylurea (MW 493.79)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Glibenclamide is a sulphonylurea which is active orally as a hypoglycaemic. Its mechanism of action is analogous to that of other related drugs (see chlorpropamide, carbutamide, tolbutamide). Glibenclamide differs from these in having a rapid but prolonged effect.

No references to the effect of glibenclamide administration in pregnancy have been found. However, as the drug is a sulphonylurea, it should not be used in pregnancy.

In the mouse, rat, and rabbit, glibenclamide had no embryofoetotoxic or

teratogenic effects [1,2]. In the mouse and rat, oral doses of 2–20–200–2000 mg/kg, given respectively from the 4th to the 13th and from the 6th to the 15th days of pregnancy had no embryofoetotoxic or teratogenic effects, except at the highest dose, when there was a slight retardation of ossification of the cervical vertebrae. This was indirectly related to the drug, in that it resulted from maternal hypoglycaemia [1]. In the mouse, rat, and rabbit, oral doses of 0.05–250 mg/kg throughout pregnancy had no embryofoetotoxic or teratogenic effects, except at doses of 250 mg (25 000 times therapeutic) when an increase in foetal resorptions was noted [2].

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Tolazamide

Tolanase,

N-(1-hexahydro-1-azepinyl)-*N'*-*p*-tolylsulphonylurea (MW 311.41)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Tolazamide is a sulphonylurea. For information on its pharmacological properties, see carbutamide, tolbutamide, chlorpropamide, etc.

Literature references indicate that tolazamide is either contra-indicated completely in pregnancy, as are other oral antidiabetics [1], or should be used only in cases of necessity [2,3].

In the rat, tolazamide was not teratogenic, but high doses were foetotoxic [2]. Oral doses of 14 mg/kg at various stages of pregnancy were neither foetotoxic nor teratogenic, but a dose of 100 mg/kg provoked a significant increase in neonatal mortality [2].

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Glicyclamide

1-cyclohexyl-3-*p*-tolylsulphonylurea (MW 296.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Glicyclamide is an oral hypoglycaemic derived from sulphonylurea. Its mechanism of action results from its ability to inhibit the degradation of insulin by the liver and to stimulate its production.

Glicyclamide is contra-indicated in pregnancy by analogy with the other sulphonylureas, although there have not been any reports of its use in pregnancy, either in the literature or from the manufacturers [1].

No experimental studies have been found on the use of glicyclamide in pregnancy in laboratory animals.

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Glicazide

Diamicron,

(methyl-1-phenylsulphonyl)-1-(perhydrocyclopenta(c)pyrrolyl-2)-3-urea
(MW 323.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

One of the sulphonylureas, glicazide is used in the treatment of non-insulin-dependent diabetes.

Like all oral hypoglycaemics, glicazide is contra-indicated in pregnancy because of its observed teratogenic effects. The manufacturers have confirmed this [1].

In the mouse, rat, and rabbit, glicazide was not embryofoetotoxic or teratogenic [1]. In the mouse, oral administration of doses 20–100–200 times therapeutic from the day of mating throughout pregnancy had no effect on fertility, gestation organogenesis, or foetal growth [1].

In Sprague-Dawley rats, oral administration of doses 6–12–24 times and 100–200 times therapeutic throughout pregnancy did not provoke malformations, changes in development, or behaviour in the foetuses and neonates. In addition, no significant changes in fertility, resorptions, number of spontaneous abortions, or neonatal weight were observed [1].

In New Zealand rabbits, oral administration of the drug at doses of 4–12–20 times therapeutic from the 6th to the 18th day of pregnancy did not cause visceral or skeletal malformations, or increase the incidence of resorptions and spontaneous abortions [1].

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Phenformin

Dibotin, *N'*- β -phenethylformamidinylaminourea (MW 241.7)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Phenformin is a biguanide with hypoglycaemic action, which stimulates anaerobic glycolysis, reduces oxidative phosphorylation, and reduces gluconeogenesis and intestinal absorption of glucose and vitamin B₁₂. It also has a ketogenic effect.

Treatment of diabetes in pregnancy with biguanides, particularly phenformin, is not definitely considered to account for the increase in early intra-uterine death, for teratogenic effects, or for poor control of glucose metabolism, which can occur in pregnancy, and which has been verified experimentally. However, because of the possibility of such side effects, phenformin is contra-indicated in pregnancy [1, 2]. A pregnant diabetic treated throughout pregnancy with insulin and phenformin at doses of 100 mg/day gave birth to a stillborn infant with micromelia, micrognathia, and abdominal and thoracic hernias. In a subsequent pregnancy, the infant was normal, following treatment with insulin alone during gestation [2]. Other authors maintain that phenformin is safe in pregnancy because, like other biguanides, it does not cross the placental barrier [3, 4].

In the rat, phenformin was teratogenic [5].

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Metformin

Glucophage, *N,N*-dimethylguanylguanidine hydrochloride (MW 165.6)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Metformin is a biguanide with a hypoglycaemic action, and with a mechanism of action analogous to that of phenformin (see page 178).

Metformin does not appear to cross the placental barrier [1]. It is, however, contra-indicated in pregnancy [4], even although there have been no reports of embryofoetotoxic or teratogenic effects related to its use [5,7,8].

In the rat, metformin was teratogenic [6,11,12]. In the mouse, it crosses the placental barrier [2]. In the rat, oral doses of 500–1000 mg/kg from the 1st to the 12th day of pregnancy caused anencephaly and anophthalmia to the extent of 0.5%, and higher doses were embryotoxic [6]. An oral dose of 250 mg/kg on the 11th and 12th days of pregnancy was teratogenic, causing cranial rachischisis and anophthalmia [10].

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Diazoxide

Eudimine,

7-chloro-3-methyl-2*H*-1,2,4-benzothiadiazine-1,1-dioxide (MW 230.7)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Diazoxide is a non-diuretic thiazide derivative which causes a hypotensive effect following arteriolar vasodilatation, accompanied by increased heart rate and output. It produces a reduction in glomerular filtration in the kidneys, a retention of water and of sodium, and an increase in the production of renin. At the metabolic level, there is a hyperglycaemia, correlated with an inhibition of insulin production by the pancreatic β cells and with an increase in hepatic glycogenolysis as a result of catecholamine release, accompanied by an increase in plasma free fatty acids. The relaxant effect of diazoxide on smooth muscle occurs at the intestinal, urethral, and uterine levels, in addition to its effect on arterioles. A diminution of cortisone production is also found after 1–2 weeks of therapy.

The side effects of diazoxide are hyperuricaemia, oedema, and increase in plasma volume which leads to cardiac imbalance, nausea, vomiting, constipation, extrapyramidal symptoms, leucopenia, thrombocytopenia, eosinophilia, and hypertrichosis (after some months of treatment).

In the plasma, diazoxide has a half life of about 28 hours and is bound to circulating protein to the extent of 90%. It competes with other drugs such as the oral anticoagulants and phenytoin. Therapeutic use of diazoxide is limited to idiopathic hypoglycaemia of infancy, and hypoglycaemia resulting from pancreatic tumours, as well as to treatment of some resistant forms of hypertension and hypertensive crisis. In obstetrics, it has been used in gestosis and in threatened premature birth.

Diazoxide crosses the placental barrier [1, 2, 11, 13, 18, 19]. The concentration in cord blood is about half that in maternal blood. Diazoxide is also found in the amniotic fluid and in neonatal urine during the first week of extra-uterine life [11]. In the sheep and goat, administration of a dose of 5 mg/kg produces foetal blood levels about half those in the mother [13]. In the goat, sheep, and pig, intravenous administration of 5 mg/kg diazoxide every 8 hours causes the appearance of the drug in foetal blood in a concentration of about half that in maternal blood, and steady state levels are reached in foetal blood after 120 minutes [12].

Diazoxide is used in the treatment of gestosis [3, 4, 5, 6, 9, 10, 16] and as a tocolytic, as well as in threatened premature birth [7, 8], without harmful effects in the mother or the foetus. Some cases have been described in which the drug was foetotoxic. Twelve patients, of whom nine had serious pre-eclampsia and three had eclampsia, were treated intravenously with 300 mg diazoxide. A rapid reduction in systolic and diastolic pressures was obtained without serious consequences to the mother or the foetus [3]. Diazoxide was administered intravenously at doses of 60–300 mg to 16 patients in normal labour in order to evaluate its tocolytic effects. In all cases, it caused a reduction in the intensity and frequency of the contractions, which was directly proportional to the dose administered. No side effects were observed in the foetus [7]. Fifteen pregnant

women at term or with threatened premature labour were treated with 60 mg diazoxide intravenously in divided doses. Inhibition of uterine contractions was obtained without any severe side effects in the mother or the foetus [8]. Diazoxide was used together with diazepam in nine patients with gestosis with good therapeutic results [9]. Four infants of patients who had taken the drug for 19–69 days during pregnancy had symptoms of alopecia. One had retarded ossification of the wrist bone. The infant did not show any changes in arterial pressure or hyperglycaemia [11].

In laboratory animals, diazoxide crossed the placental barrier [13, 18, 19]. In the monkey, its tocolytic action was demonstrated [14, 17]. In the sheep and goat, its diabetogenic effect [13] or its hyperglycaemic effect in the foetus [19] was shown in the absence of any significant circulatory changes [19].

In the monkey, diazoxide was administered at a dose of 0.065 mg/kg/minute for 4 hours to inhibit uterine contractions in the event of premature birth. It caused maternal tachycardia without circulatory changes or acid–base disturbances in the foetus [14].

Diazoxide was administered to seven sheep of gestational age between the 94th and 131st day at rapid intravenous doses of 5 mg/kg/minute or at a dose of 0.06 mg/kg/minute for a period of 3 hours. Rapid administration caused maternal tachycardia with hypotension and significant diminution of uterine blood flow, while slow administration did not produce these effects. In both cases, no signs of foetal stress were observed [15]. In the goat and the sheep, diazoxide, administered from the 110th to the 115th day of pregnancy caused the destruction of foetal pancreatic cells. At the same time, a significant foetal hyperglycaemia was noted [13].

In the goat, the sheep, and the pig, diazoxide administered intravenously at a dose of 5 mg/kg every 8 hours caused a significant foetal hyperglycaemia. In these three species, 75% of the neonates presented with diabetes. In aborted or dead foetuses, histological examination within 5 days of birth demonstrated a degeneration of the pancreatic beta cells. The surviving neonates presented with hyaline membrane disease [18].

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Part 7

Analgesics, Antipyretics and anti-inflammatory drugs

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Two categories of analgesics may be distinguished, which differ in their intensities of action. In intense pain, only the narcotic analgesics with central action are effective, and these are described among drugs active on the central nervous system (see Vol. 1). The analgesics which are dealt with here are indicated in the therapy of mild or moderate pain. These drugs all have antipyretic and anti-inflammatory actions based on a common mechanism which involves inhibition of biosynthesis of prostaglandins at central or peripheral levels. Many symptoms of inflammation are linked to this biosynthesis. For this reason, the analgesic action of these products appears only when the pain is caused by prostaglandin production, and is always accompanied by an anti-inflammatory or antipyretic action.

The analgesic, anti-inflammatory, and antipyretic drugs inhibit cyclo-oxygenase, the enzyme which catalyses the transformation of arachidonic acid into various components of the prostaglandin system. They thus tend to block prostaglandin-dependent uterine contractility and the dilatation which takes place spontaneously in labour. These drugs pass to the foetus, and affect regulation of basal tone, causing constriction of the pulmonary blood vessels and the arterial ducts. Chronic administration causes hypertrophy of nasal smooth muscle and a persistent reduction in the calibre of pulmonary blood vessels, which reduces neonatal oxygenation at birth.

On the basis of their chemical structure, the analgesic-antipyretics may be subdivided into aniline, anthranyl, pyrazole, phenylalkanoyl, salicyl, and various other derivatives. The anti-inflammatory drugs are described among the steroid hormones (see cortisone, page 74), although these do not have an analgesic-antipyretic action because they block inflammation without inhibiting prostaglandin synthesis.

The following drugs are discussed here:

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Paracetamol	NC	187
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	Recommendation	Page
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Salamidoacetic acid	P	206
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Dipirocetile	P	207
Sodium gentisate	P	208
Morpholine salicylate	P	208
Aloxaprin	P	208
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Ibuprofen	P	210
Ketoprofen	P	210
Indomethacin	P (C during lactation)	211
Sulindac	P	215
Naproxen	P	215
Diclofenac	P	217
Indoprofen	P	217
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<i>Miscellaneous antirheumatics</i>		
Benzidamin	P	219
Diphthalone	P	219
Tolmetin sodium	P	220
Methiazinic acid	P	221

So far as prescription of paracetamol is concerned there are no restrictions on its use during pregnancy, nor on the use of the pyrazole derivatives, benzidamin, or diphthalone. The anthranil derivatives should be used with care, because of their toxicity, and salicylic acid and ibuprofen should also be used prudently. Indomethacin is contra-indicated during lactation.

At the approach of labour, inhibition of prostaglandin synthetase at the uterine level, which is a property of all these drugs, with the exception of paracetamol, often hinders the start of labour or its arrest. This action is used in the treatment of threatened premature labour, with the administration of large doses of salicylates or indomethacin.

There is insufficient information available for a reliable judgement on the use of the following drugs in pregnancy: feniramidol (page 222), aminopropylone, niapirin, dinoranodipyrin, salicylamidophenazone, chlortenoxazin, oxycincophen, isophthaloic acid, indosamide, sulphenazone, fenbutanidol, benzopiperilone (pages 222–223).

Although the prostaglandins do not belong to this group of analgesic-antipyretics, and anti-inflammatories, we feel that a consideration here of their mechanism of action may be useful in clarifying the mechanisms of action of the above drugs.

1. ANILINE DERIVATIVES

Paracetamol

Calpol, Panadol, etc.,

N-acetyl-para-aminophenol (MW 151.16)

Not contra-indicated in pregnancy.

Acetyl-para-aminophenol is an active metabolite of acetanilide, and of phenacetin, and has both analgesic and antipyretic actions. Its anti-inflammatory action is weak. It does, in fact, inhibit prostaglandin synthetase, but only at the cerebral and not the peripheral level. It is without the metabolic effects characteristic of the salicylates, and thus does not produce gastric irritation, increase in uric-urea, etc. (see acetylsalicylic acid, page 201).

Paracetamol is rapidly absorbed in the digestive tract, is partially bound to plasma proteins, conjugated in the liver with glucuronic and sulphuric acids, and excreted in the urine. It is partly hydroxylated and de-acetylated, leading to a compound which is hepatotoxic and causes methaemoglobinaemia. Paracetamol can increase the hypoprothrombinaemia caused by the oral anticoagulants, and can give rise to thrombocytopenia and haemolytic anaemia. Its low toxicity makes it useful as an analgesic and antipyretic, particularly in patients who are allergic to aspirin.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2].

No experimental studies have been described on the use of paracetamol in pregnancy in laboratory animals.

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2. ANTHRANYL DERIVATIVES

Mefenamic acid

Ponstan,

N-(2,3-xylyl)anthranilic acid (MW 241.28)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

The derivatives of anthranilic acid, an amino derivative of salicyclic acid, have anti-inflammatory activity. One of the most active compounds in this group is mefenamic acid. Its mechanism of action is analogous to that of the salicylates (see acetylsalicylic acid, page 201), but it has more serious side effects, including irritation of the mucosa of the digestive tract, myeloinhibition, and potentiation of oral anticoagulants.

There are no absolute contra-indications to the use of mefenamic acid in pregnancy [1]. Its toxicity should discourage its use in the neonatal period, and it requires careful administration during pregnancy. Chronic administration may delay the initiation of labour and alter foetal vasal tone, analogously to other inhibitors of prostaglandin biosynthesis (for further details, see indomethacin, page 211).

After administration of 750 mg/day mefenamic acid to ten women, the drug was found in breast milk in concentrations varying from 17–21 $\mu\text{g/ml}$ [2].

In the rat, mouse, and rabbit, mefenamic acid showed foetotoxicity but was not teratogenic, even at high doses [1]. In the rat, doses of 7–9 times therapeutic from the 8th to the 16th day of pregnancy increased perinatal mortality and delayed parturition. No malformations were observed [1]. In the mouse, doses of 5–6 times therapeutic from the 8th to the 16th day of pregnancy had the same effects [1]. In the rabbit, doses of 10–12 times therapeutic on the 10th to the 18th day of pregnancy were foetotoxic but not teratogenic [1].

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Flufenamic acid

Meralen,

2-(3-trifluoromethyl-phenylamino)-benzoic acid (MW 281.24)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Flufenamic acid possesses both analgesic and anti-inflammatory activity. The latter effect differs from that of the glucocorticoids in that it is independent of the hypophysis—adrenal axis, and does not appear to cause depressant effects on tissue growth.

No reports of harmful effects have been found in the literature, and the manufacturers had no such documentation either. Despite this, they maintain that the use of flufenamic acid in pregnancy is not advisable, although they do not believe that it is either embryofetotoxic or teratogenic [1]. As a result of recent findings on the antiprostaglandin action of these drugs, it is, however, justifiable to use this substance with care in pregnancy (see indomethacin, page 211).

Flufenamic acid passes into breast milk in small amounts only [2].

No experimental studies have been described on the use of flufenamic acid in pregnancy in laboratory animals, and the manufacturers have no data on this [1].

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Floctafenin

2,3-dihydroxypropyl-2((8-(trifluoromethyl)-4-quinolyl)amino)benzoate
 (MW 406.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Floctafenin is an anthranlyl derivative with a mainly analgesic action. It is rapidly absorbed from the digestive tract, and equally rapidly metabolized in the

liver by hydrolysis, hydroxylation, and glucuronide conjugation. It is eliminated in the urine and bile. The analgesic and anti-inflammatory actions of floctafenin are mediated by an inhibitory effect on the biosynthesis of prostaglandins, to an extent comparable to that of indomethacin.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we maintain that because of the anti-prostaglandin action of floctafenin, it should be used with care in pregnancy (see indomethacin, page 211).

In the mouse, rat, and rabbit, floctafenin was not teratogenic, but had embryotoxic activity at high doses [1]. In the mouse, oral doses of 80–160–320 mg/kg from the 6th to the 17th day of pregnancy were foeto-toxic at the highest dose, and lethal for the pregnant animals [1]. In the rat, doses of 40–80–160 mg/kg from the 6th to the 18th day of pregnancy were not embryofoetotoxic or teratogenic [1]. In the rabbit, similar doses from the 6th to the 24th day of pregnancy increased the number of resorptions and intra-uterine deaths only at the higher doses [1].

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Glafenin

2,3-dihydroxypropyl-*N*-(7-chloro-4-quinolyl)anthranilate (MW 372.33)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Glafenin is an anthranil derivative with a stronger analgesic than anti-inflammatory action. It is rapidly absorbed orally and equally rapidly eliminated, mainly in the urine. The side effects of glafenin are slight, and occur mainly in the stomach, the liver, the blood, and the eyes.

Administered from the 6th to the 20th week of pregnancy or in later periods of pregnancy, in the treatment of threatened premature birth, glafenin had no harmful effects on the foetus or the mother [1]. In labour it is equally free of harmful effects [1, 2, 3, 4, 5], while it may actually reduce the duration of labour [3]. Administration of 400 mg initially, followed by doses of 200 mg every hour, in 190 women during labour produced good analgesia, with no side effects in the mother or the foetus [2]. Glafenin was administered to 500 women in labour at a dose of 500 mg rectally. It reduced the duration of labour and

relaxed the cervix, in addition to its analgesic effect [3]. In 26 patients, administration of the drug in labour accelerated its progress without harming the foetus [4]. In 193 women treated with glafenin, there were no serious side effects in the mother or the foetus [5].

Despite these favourable reports, we believe that glafenin should be used with care in pregnancy because it has antiprostaglandin activity similar to that of indomethacin (see page 211).

In the rat, mouse, and rabbit, glafenin was not teratogenic when administered throughout pregnancy at doses of 10–100 mg/kg [6].

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3. PYRAZOLE DERIVATIVES

Phenylbutazone

Butazolidin, Butacote, Parazolidin,

3, 5-dioxo-1, 2-diphenyl-4 *n*-butylpyrazolidine (MW 308.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Phenylbutazone is a pyrazolone derivative with anti-inflammatory, antipyretic, and analgesic actions, similar to some extent to those of the salicylates. Phenylbutazone inhibits the biosynthesis of the prostaglandins and of mucopolysaccharides, uncouples oxidative phosphorylation, and inhibits the enzymes of the tricarboxylic acid cycle, thus reducing the production of energy and interfering with tubular reabsorption of uric acid.

Phenylbutazone is rapidly absorbed in the gastrointestinal tract, is almost completely bound to plasma proteins, is transformed in the liver in part to oxyphenylbutazone, and is slowly eliminated in the urine. Numerous drugs interact with phenylbutazone by means of a competitive mechanism of binding with plasma proteins (other anti-inflammatory drugs, oral anticoagulants, oral hypoglycaemics, sulphonamides). Simultaneous administration of phenylbutazone and these drugs increases the free fraction, and thus the intensity of action (e.g., the exaggerated anticoagulant effect of a coumarin administered with phenylbutazone). There could also be competition for hepatic hydroxylation.

The principal side effects of phenylbutazone occur in the digestive tract (nausea, vomiting, diarrhoea, ulcers), in the haemopoietic organs (anaemia, leucopenia, thrombocytopenia), and in the liver.

Phenylbutazone crosses the placental barrier, reaching a concentration of $\frac{1}{2} - \frac{1}{10}$ th that of maternal blood in the foetus [1, 2, 3]. According to some workers, the drug passes into the milk in minimal quantities [3, 9, 10]. Others, however, believe that phenylbutazone does not pass into breast milk [2]. During such investigations, no harmful effects were reported in the foetus, the mother, or on the pregnancy. However, the drug should be used with care in pregnancy because of its action on prostaglandin metabolism (see indomethacin, page 000).

In the rat and rabbit, phenylbutazone was neither embryofetotoxic nor teratogenic, except at extremely high doses. In the rat, doses of 3.3 mg/kg for 8 days during pregnancy had no harmful effects on the foetus [4]. Oral doses

of 5–15 and 45 mg/kg given twice from the 18th day of pregnancy until parturition lengthened the duration of pregnancy and of labour, and increased postnatal mortality only at the highest dose [11].

In the rat and rabbit, doses of 42 and 50 mg/kg respectively during the period of organogenesis were not teratogenic [7]. In the rabbit, doses of 30–60 mg/kg from the 1st to the 20th day of pregnancy did not reduce fertility. However, the drug did cause slight malformations (anomalies of the vertebrae, umbilical hernia) in a small number of cases. These experiments did not exclude the possibility of some embryotoxic effects, which appeared at higher doses, between $\frac{1}{5}$ th and $\frac{1}{10}$ th of the LD₅₀ of 270 mg/kg [6]. Phenylbutazone at oral doses of 5–15–45 mg/kg given twice from the 28th day of pregnancy until parturition shortened the duration of pregnancy but did not affect labour or increase perinatal mortality [11].

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Oxyphenylbutazone

Tanderil, Tandacote, Tandalgesic,
1-phenyl-2-(*p*-hydroxyphenyl)-3, 5-dioxo-4-*n*-butylpyrazolidine
monohydrate (MW 342.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Oxyphenylbutazone is the product of hepatic hydroxylation of phenylbutazone, and has the same pharmacological action, binds to plasma proteins, and is slowly eliminated in the urine. Its mechanism of action and side effects are the same as those of phenylbutazone (see page 192), but it causes less gastric irritation.

Oxyphenylbutazone crosses the placental barrier and reaches concentrations in foetal blood of between 10 and 80% of those in maternal blood [1]. It does not pass into amniotic fluid [1]. There have been no reports of harmful effects on the foetus, and the manufacturers have confirmed this [2]. However, we maintain that oxyphenylbutazone should be used with care in pregnancy because of its action on prostaglandin metabolism (see indomethacin, page 211). Administration of oxyphenylbutazone in labour causes no side effects in the mother or the foetus, and therefore it may be used in the last part of pregnancy [1,2]. It does not produce analgesia in the first stage of labour [1].

Passage of oxyphenylbutazone into breast milk has been shown in only two out of 55 cases, following administration of a total dose of 1200 mg. The drug may therefore be safely used in lactating women [1].

No experimental studies have been described on the use of oxyphenylbutazone in pregnancy in laboratory animals, and the manufacturers also have no such information [2].

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Monophenylbutazone or mofebutazone

(MW 232.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Monophenylbutazone is an analogue of phenylbutazone and is believed to represent an improvement on the original drug. Its pharmacodynamic characteristics are similar to those of phenylbutazone (see page 190).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we believe that monophenylbutazone should be used with care in pregnancy because of its effect on prostaglandin metabolism (see indomethacin, page 211).

In the rat and rabbit, monophenylbutazone was neither embryofoetotoxic nor teratogenic, and it did not reduce fertility [1,2,3]. In the rabbit, subcutaneous doses of 60–150 mg/kg in the first 20 days of pregnancy did not affect fertility and were not teratogenic [1]. In the rat, doses of 33 mg/kg subcutaneously in the first 18 days of pregnancy likewise did not affect fertility [2].

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Nifenazone

4-nicotinamido-2-phenyl-1,5-dimethyl-3-pyrazolone (MW 308.33)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Nifenazone is a derivative of pyrazolone with anti-inflammatory and anaesthetic actions, but with some hepatic and medullary toxicity, and with ulcerogenic properties.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1]. However, we believe that nifenazone should be used with care in pregnancy because of its effect on prostaglandin metabolism (see indomethacin, page 211).

No experimental studies have been described on the use of nifenazone in pregnancy in laboratory animals.

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Feprazone or phenylprenazone

Methrazone,

4-prenyl-1,2-diphenyl-3,5-pyrazolidindione (MW 320.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Feprazone is an orally active pyrazole derivative with a mainly anti-inflammatory action. Compared to phenylbutazone, it has similar antipyretic, analgesic, and anti-inflammatory activities, but possesses a smaller ulcerogenic effect.

Feprazone administered during labour has no notable side effects on the mother or the neonate [1]. It crosses the placental barrier with some delay, and reaches the foetal plasma in a concentration equal to 20% of that in the maternal blood by 6 hours, and 44% at 18 hours [1]. Even though there have been no reports of embryofoetotoxic or teratogenic effects, we believe that feprazone should be used with care in pregnancy because its mechanism of action is similar to that of indomethacin (see page 211).

Feprazone does not pass into breast milk, even after repeated administration [2].

In the rat and rabbit, feprazone had no embryofoetotoxic or teratogenic effects [3]. In the rabbit, oral doses of 50 mg/kg and 100 mg/kg from the 1st to the 29th day of pregnancy did not cause harmful effects to the foetus [1]. In the rat, doses of 50–100–200 mg/kg/day from the 1st to the 19th day of pregnancy did not produce any significant effects in the foetus [3].

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Ketophenylbutazone or kebuzone

1,2-diphenyl-4- γ -ketobutyl-3,5-pyrazolidindione (MW 322.37)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Ketophenylbutazone is a pyrazolone derivative which is less toxic than phenylbutazone (see page 192).

No reports have been found of harmful effects to the foetus, the mother, or the pregnancy, and the manufacturers have confirmed this [1]. However, we think that ketophenylbutazone should be used with care in pregnancy because of its effects on prostaglandin metabolism (see indomethacin, page 211).

No experimental studies have been described on the use of ketophenylbutazone in pregnancy in laboratory animals, and the manufacturers also have no data on this aspect [1].

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Pirazanone

1,2-diphenyl-3,5-dioxo-4-butylpyrazolidine hexahydropyrazine (MW 394.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Pirazanone has a pyrazolidine structure and pharmacological characteristics similar to those of phenylbutazone (see page 192).

No reports have been found of harmful effects to the foetus, the mother, or the pregnancy. However, we believe that pirazanone should be used with care in pregnancy because of its effect on prostaglandin metabolism (see indomethacin, page 211).

In the rat, pirazanone had no embryofoetotoxic or teratogenic effects [1]. Oral doses of 25–50 mg/kg before and throughout pregnancy caused no damage to the foetus [1].

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Azapropazone or apazone

Rheumox,

5-dimethylamino-2,3-dihydro-9-methyl-2-propyl-1*H*-pyrazol(1,2- α)-(1,2,4)-benzotriazine-1,3-dione dihydrate (MW 336.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Azapropazone is a pyrazolone derivative with anti-inflammatory and analgesic properties. As with similar products, it can cause side effects on the digestive tract, and affect renal function and blood cells.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, azapropazone should be used with care in pregnancy because of its mechanism of action, which involves inhibition of prostaglandin synthesis (see indomethacin, page 211).

In the mouse, rat, and rabbit, azapropazone at high doses caused embryofoetotoxic effects but was not teratogenic. In the rat, oral doses of 100–200 mg/kg throughout pregnancy reduced foetal growth and weight gain in pregnant animals [1]. Oral doses of 100 mg/kg from the 1st to the 19th day of pregnancy, or oral doses of 200 mg/kg from the 8th to the 12th day of pregnancy were not embryofoetotoxic or teratogenic [2]. According to other authors, azapropazone had no teratogenic effects at doses of 2.5–5 times therapeutic in man, and did not affect fertility [3].

In the mouse, oral administration of the drug at doses of 100–300–600 mg/kg throughout pregnancy caused a reduction in weight gain in pregnant animals and in foetal growth. A retardation of ossification was also observed at lower doses [1]. In the rabbit, oral doses of 100 mg/kg and 400 mg/kg from the 6th to the 8th day of pregnancy did not affect foetal development or have teratogenic effects.

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Aminophenazone or aminopyrine or amidopyrine or pyramidone
dimethylamino-phenyldimethyl-pyrazolone (MW 231.29)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Aminophenazone is one of the oldest of the analgesic–antipyretic–anti-inflammatory drugs derived from pyrazolone. Its therapeutic action is similar to that of the salicylates, but it has no uricosuric or gastric irritant effects. In addition, it does not affect metabolism of acid–base equilibrium (see acetylsalicylic acid, page 201). The increased myelotoxicity of aminophenazone limits its use, since this is an allergic reaction which develops in only 0.1–0.01% of patients, which leads to agranulocytosis – which can be fatal. For this reason, the drug is no longer used in countries such as the USA, where it was prohibited in 1938. Furthermore, it should be considered a potential carcinogen. When administered orally during meals, it can react with nitrites in the food to form dimethylnitrosamines. This reaction is catalysed by thiocyanate which is present in the saliva of many smokers [13]. There are, however, no certain demonstrations of the role of nitrosamines in the aetiology of human cancer, and the

formation of these substances in the stomach may be prevented by using substances not metabolized in the stomach, as well as by the use of aminophenazone at times other than mealtimes or in association with ascorbic acid.

Aminophenazone crosses the placental barrier [1, 2, 3, 5]. Administration of the drug in pregnancy does not produce embryofetotoxic or teratogenic effects [1, 4, 5, 6, 9, 10, 11, 12]. It has also been shown that concentrations reached in foetal blood were 2–10 times less than those in maternal blood [5]. However, since the use of aminophenazone is associated with many problems even in the non-pregnant patient, it seems advisable to contra-indicate its use in pregnancy.

The passage of aminophenazone into breast milk has not been established with certainty [5].

In the rat, mouse, and rabbit, no harmful effects were reported in the pregnant animals or the foetuses when doses of 5–6 times therapeutic were administered [7].

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Noramidopyrine or metamizole or dipyrone

2, 3-dimethyl-1-phenyl-5-pyrazolonyl-*N*-methylamino methanesulphonate monohydrate of sodium (MW 351.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Noramidopyrine is the sodium methane sulphonate of aminophenazone. It has the same properties and side effects (agranulocytosis, nephrotoxicity, etc. — see page 198). Noramidopyrine is administered intravenously during

attacks of asthma which do not respond to other therapy, such as inhibitors of the biosynthesis of prostaglandin $F_2\alpha$, or in association with antispastics, or in colicky pain resulting from spasms of the intestine. This method of administration can lead to anaphylactic shock in patients who are particularly sensitive.

Noramidopyrine has been used in labour, because of its analgesic action. There have been no reports of side effects in the mother or the neonate [1]. However, by analogy with aminophenazone, we believe that the drug should be contra-indicated in pregnancy.

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4. SALICYLATES

Acetylsalicylic acid and salicylates

Aspro, Veganin, Codis, etc.

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Acetylsalicylic acid is the most widely used of the salicylates, and is commonly taken without medical prescription.

The pharmacological actions of the salicylates are: analgesia (especially against pain of light or medium intensity and of non-visceral origin), antipyresis, hyperventilation following stimulation of the respiratory centre and of respiratory alkalosis, peripheral vasodilation, increase in cardiac activity, gastro-intestinal irritation, hydrocholeresis, reduction of sideraemia, reduction of VES, reduction in the half life of erythrocytes especially in conditions of lack of glucose-6-phosphate dehydrogenase, increase in the bleeding time by inhibition of platelet aggregation, increase in uricosuria, inhibition of mesenchymal inflammatory processes, increase in catecholamine release and of glucocorticoids, diminution of thyroid activity, keratolysis, and irritation of the epithelium (when used locally).

The metabolic and cellular action of the salicylates is very complex: they inhibit prostaglandin synthetase peripherally, and thus the formation of chemical mediators of pain and of inflammation (bradykinin, histamine, 5-HT); they also inhibit the biosynthesis of the prostaglandins at the cerebral levels, which are stimulated by pyrogens, and thus block fever; they increase oxygen consumption and the production of carbonic anhydride, thus stimulating cellular respiration, by uncoupling of oxidative phosphorylation. They reduce the synthesis of proteins, accelerate catabolism, and diminish tubular resorption of the amino acids. They stabilize the lysosomal membranes of leucocytes and impede the liberation of lysing enzymes which are also damaging to articular tissues and which liberate prostaglandins from arachidonic acid. They modify the biosynthesis and thus the composition and structure of the mucopolysaccharides of the fundamental connective substances, which represent a barrier to the spreading of infection and of fever. They increase peripheral (cellular) utilization of glucose and inhibit the enzymes of neoglucogenesis. They block the incorporation of acetate into fatty acids, they inhibit lipolysis, they increase

oxidation of fatty acids and of the ketonic bodies, and they diminish plasma lipid fractions.

The salicylates, administered orally, are absorbed in the primary digestive tract but irregularly by the rectal route; they are distributed in all tissues and organic liquids with the exception of bile.

Their linkage with protein plasma varies from 50 to 90% in accordance with the presence of other substances and with pH.

Acetylsalicylic acid is rapidly hydrolyzed in plasma, liver, and erythrocytes, but this hydrolysis is not necessary for its pharmacological action, as was once believed. On the contrary, acetylsalicylic acid can acetylate numerous plasma and hormonal proteins. The salicylates are inactivated in liver microsomes and mitochondria, by conjugation with glycine and glucuronic acid, or alternatively they are oxidized and eliminated in the urine.

Salicylic acid and the salicylates rapidly cross the placental barrier [6, 14, 15, 23, 39, 60, 61]. The teratogenic action of the salicylates has been widely discussed. Some authors, basing their conclusions on retrospective assessments which are often of limited range, have advanced the hypothesis that their chronic administration in the first months of pregnancy can give rise to malformations [1, 2, 3, 4, 5, 6, 7, 56, 62, 67]. Others, however, have denied this relationship [8, 9, 47, 48]. On a retrospective study on 32 164 patients who had taken acetylsalicylic acid during pregnancy (14 864 in the first 4 months and of these, 5128 for at least 1 week), the percentage of malformed neonates was similar in patients who had taken the drug (a) in the first months (b) throughout pregnancy, and (c) in controls [47]. Similarly, acetylsalicylic acid taken in pregnancy does not appear to cause an increase in perinatal or neonatal mortality [48]. A teratogenic action of salicylates has not so far been demonstrated, at least at therapeutic doses [10, 11, 58, 59, 60, 61].

Acetylsalicylic acid and its analogues can change the duration of pregnancy. High doses in the last months of gestation significantly increased the incidence of delayed postnatal maturity and lengthened the duration of labour [12, 13, 58, 59, 71, 72]. This phenomenon may be linked to the inhibitory action of acetylsalicylic acid on prostaglandin biosynthesis, as occurs with other anti-inflammatory drugs. Acetylsalicylic acid, when taken during pregnancy, may cause a decrease in oestrioluria ($39.44 \pm 23.9\%$), probably due to interference with conjugation of foetal oestriol, or to some biological effect on prostaglandin synthesis [49]. It has been demonstrated that acetylsalicylic acid interferes with enzymic hydrolysis of the urinary steroids, because when they are conjugated with glucuronic acid, they compete with the latter for the hydrolyzing enzyme [50, 51].

Acetylsalicylic acid has been administered at a dose of 600 mg every 6 hours to patients who were to undergo a therapeutic abortion in the second trimester. In nulliparous women, labour was slowed, but in those with previous pregnancies there was no significant difference. This may be explained by the increased

cervical tone in nulliparous women, or by the inadequacy of the dose necessary to 'cover' the effect of oxytocin in those women with previous pregnancies [57]. The capacity of acetylsalicylic acid to inhibit uterine contractions could have therapeutic implications in the treatment of threatened premature birth [57].

In pregnancy, acetylsalicylic acid and the salicylates in general when taken in toxic doses, for example with the aim of suicide, may cause foetal death [14] or serious foetal poisoning [68]. This may be improved by complete blood transfusion [15]. At very high doses, the drug may cause abortion [16, 17]. This embryofoetotoxic action occurs as a result of inhibition of platelet aggregation, a reduction in factor XII (Hageman factor), discernible also in the neonate [18, 19, 20], and a lack of vitamin K [14]. For this reason, it is also advisable to limit the use of acetylsalicylate in the last months of pregnancy.

The salicylates pass into breast milk in a quantity which is proportional to the administered dose [63, 67, 69].

In the rat and mouse, salicylic acid and its analogues were teratogenic [21, 22, 23, 24, 25, 26, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 52, 53, 54, 55, 65, 66]. The mechanism of teratogenesis of this drug is not completely known. It may be due to inhibition of the synthesis of acid mucopolysaccharides [21], a diminution of RNA-polymerase with consequent inhibition of RNA synthesis [22], or an alteration of the lysosomes [23] or of the structure of the glycosaminoglycans [24]. The teratogenic effect is linked in particular to the functional groups in the aromatic ring [25] and is potentiated by benzoic acid, widely used as a food additive [26].

In the rat, subcutaneous doses of 60–180 mg on the 9th, 10th, or 11th days of pregnancy caused teratogenic effects, including cranioschisis, exencephaly, hydrocephalus, facial schisis, ocular defects, gastroschisis, and irregularities of the vertebrae and ribs [52]. Subcutaneous administration of salicylates at doses of 200–250 mg/kg from the 10th to the 19th day of pregnancy caused teratogenic effects [65]. Acetylsalicylic acid and the salicylates in general were foetotoxic in the last part of pregnancy in the mouse, rat, rabbit, macaque mulatto, and sheep [27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 52, 54, 64, 70]. In the rat, acetylsalicylic acid and the salicylates prolonged labour and increased perinatal death [29, 30]. Doses of 100–600 mg/kg were foetotoxic and teratogenic, producing skeletal malformations and anomalies of the central nervous system and digestive and urinary tracts [33, 34, 35, 36, 37, 38]. Intramuscular doses of 50–500 mg/kg from the 12th to the 14th day of pregnancy were embryofoetotoxic, causing an increase in foetal resorptions [64].

In the mouse, intramuscular administration of 10 mg/kg salicylate on the 12th or 13th day of pregnancy caused skeletal malformations of the limbs [66]. Acetylsalicylic acid and the salicylates caused intra-uterine death of the foetus, haemorrhage [27], and premature birth [28]. Oral doses of 100–750 mg/kg from the 6th to the 14th day of pregnancy were foetotoxic and teratogenic, causing

skeletal malformations and anomalies of the central nervous system and digestive tract [33, 34, 39, 40, 41].

In the rabbit, doses of 100–300 mg/kg from the 5th to the 16th day of pregnancy were foetotoxic and teratogenic, causing malformations of the skeleton and of the cardiovascular system [34, 37, 40, 42, 43].

In the macaque mulatto, an oral dose of 20–600 mg/kg from the 18th day of pregnancy until term was foetotoxic, but the teratogenicity of the drug was controversial [44, 45, 46].

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Choline salicylate

Audax, Teejel,

(2-hydroxyethyl)-trimethylammonium salicylate (MW 241.28)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Choline salicylate has antipyretic, analgesic, and antirheumatic properties equal to those of the salicylates (see page 201).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3]. However, as the drug is related to the salicylates, we would advise caution in its use in pregnancy (see page 201).

No experimental studies have been found on the use of choline salicylate in pregnancy in laboratory animals.

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Salamidoacetic acid

2-carboxamido-phenoxyacetic acid (MW 195.18)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Salamidoacetic acid is a water-soluble salicylate which is less irritant and may be administered orally or parenterally. Its effects are similar to those of the salicylates (see page 201).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1]. Despite this, we advise caution in the use of salamidoacetic acid in pregnancy, since it is related to the salicylates (see page 201).

In the rat, salamidoacetic acid had no embryofetotoxic or teratogenic effects. Only at very high doses was there a slight fetotoxic effect. Doses of about 6 times therapeutic given intramuscularly from the 5th to the 15th day of pregnancy had no effect on the number of abortions, the weight of the live neonates, or the number of perinatal deaths. At doses 20 times therapeutic,

administered in the same way, there was an increased incidence of abortions and underdeveloped foetuses, but there were no teratogenic effects [1].

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Salicylamide

Delimon, Intralgin (MW 137.13)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Salicylamide is an analgesic which is comparable to salicylic acid (see page 201), but with a lesser antipyretic action. It does, however, have a choleric action.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1]. However, as salicylamide is related to the salicylates, its use in pregnancy should be carefully controlled (see page 201).

In the hamster, salicylamide was embryofoetotoxic and teratogenic. Oral doses of 65 mg twice a day from the 6th to the 18th day of pregnancy were embryofoetotoxic and teratogenic, causing umbilical hernia, gastroschisis, oedema, and haematoma. Administration of the same oral dose from the 9th to the 11th day of pregnancy was teratogenic [2].

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Dipirocetile

2,3-dihydroxybenzoic acid diacetate (MW 238.19)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Salicylic acid is partially oxidized in the organism to 2,3-dihydroxybenzoic

acid. This metabolite is then eliminated in the urine. 2,3-dihydroxybenzoic acid diacetate is used as an antirheumatic instead of salicylates (and has the same indications and contra-indications - see page 201).

Sodium gentisate

sodium 2,5-dioxybenzoate (MW 176.04)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Some of the administered salicylic acid is oxidized in the organism to gentisic acid, which is then eliminated in the urine. Sodium gentisate may be administered to patients who cannot tolerate salicylates. The indications and contra-indications are similar to those for the salicylates (see page 201).

Morpholine salicylate

(MW 225.26)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Morpholine differs from sodium salicylate by virtue of its greater tolerability following oral administration (see salicylates, page 201).

Aloxiprin

Palaprin Forte, polymeric condensation product of aluminium oxide and acetylsalicylic acid (MW ~1013)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Aloxiprin is a polymeric condensation product of acetylsalicylic acid and

aluminium oxide, it passes unaltered through the stomach, and is slowly dissociated in the intestine. Release of acetylsalicylic acid is gradual, and gastric irritation is thus avoided. The pharmacological properties of aloxiprin are identical to those of acetylsalicylic acid (see page 201).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, as aloxiprin is related to the salicylates, it should be used with care in pregnancy (see page 201).

No experimental studies have been described on the use of aloxiprin in pregnancy in laboratory animals.

5. PHENYLALKANOIC DERIVATIVES

Ibuprofen

Brufen, 2-(4-isobutyl-phenyl)-propionic acid (MW 206.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Ibuprofen is a non-steroid anti-inflammatory drug with analgesic and antipyretic properties. Its principal side effect is its ulcerogenic action, which, at least in experimental animals, appears to be aggravated in pregnancy [1].

Although certain authors [2] consider ibuprofen to be safe in pregnancy, others [3] maintain that it should be avoided in the last stages because of its inhibitory action on prostaglandin biosynthesis.

In the rat and rabbit, ibuprofen crossed the placental barrier [1], and at doses of up to $\frac{2}{3}$ rds therapeutic it was not teratogenic [3]. In the rabbit, oral doses of 7.5–20–60 mg/kg (the therapeutic dose is 1–1.5 g/day) throughout pregnancy caused gastrointestinal ulceration and a reduction in weight gain of the pregnant animals, particularly at the higher doses [1]. There were no apparent harmful effects on the foetus.

In the rat, similar oral doses throughout pregnancy were harmful to the pregnant animals, causing reduction in weight gain, but only at the highest doses. There were no embryofetotoxic or teratogenic effects even at ulcerogenic doses [1].

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Ketoprofen

Orudis, 2-(3-benzoylphenyl)-propionic acid (MW 264.28)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Ketoprofen is a synthetic product with anti-inflammatory, antipyretic, and analgesic properties.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. Some authors, however, advise that ketoprofen should be used with care in the first trimester, because of insufficient clinical evidence of its safety [1]. Furthermore, according to recent observations on drugs with antiprostaglandin activity, its chronic use in pregnancy is not recommended.

In the mouse, rat, and rabbit, ketoprofen was not embryofetotoxic or teratogenic [2]. In the mouse, oral doses of 3–6–12 mg/kg from the 5th to the 15th day of pregnancy had no harmful effects on the foetus, and did not affect postnatal development [2]. In the rat, oral doses of 3–6–9 mg/kg from the 5th to the 15th day of pregnancy had no side effects [2]. In the rabbit, oral doses of 3–6–12 mg/kg from the 6th to the 16th day of pregnancy were not embryofetotoxic or teratogenic. At high doses, ketoprofen was slightly embryotoxic, increasing foetal resorption [2].

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Indomethacin

Indocid, Imbrilon,

1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-indole-3-acetic acid (MW 357.78)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		C

To be used with care in pregnancy and is contra-indicated during lactation.

Indomethacin is a powerful anti-inflammatory, antipyretic, and analgesic drug, with an indole structure. Indomethacin inhibits the synthesis of prostaglandins and thromboxanes, linking reversibly to the apo-enzyme of cyclo-oxygenase, which uncouples phosphorylation in the mitochondria and reduces leucocyte mobility, as does colchicine.

Indomethacin is rapidly absorbed from the digestive tract and binds to plasma and tissue proteins to the extent of 90%. It has a plasma half life of about 10 hours, and is transformed into inactive metabolites by demethylation and de-acetylation. Two thirds are eliminated in the urine in the form of conjugated glycuronides, and one third in the faeces. The side effects of

indomethacin are observed mainly in the central nervous system (cephalea, giddiness, buzzing, mental confusion, visual disturbances), the digestive tract (anorexia, nausea, diarrhoea, peptic ulcer), the kidneys (papillary necrosis), haemopoiesis (anaemia, agranulocytosis, thrombocytopoenia), and the liver. Intravenous administration may cause hypotension.

Indomethacin crosses the placental barrier in the rabbit [1], the dog [2], and on the basis of its biological effects probably also in the human. In the rabbit, a single dose of 2 mg/kg causes the rapid appearance of the drug in foetal blood and in the amniotic fluid. In foetal blood, the concentration is about half that in maternal blood after about 2 hours, and in amniotic fluid about $\frac{1}{10}$ th [1]. In the dog, a dose of 1 mg/kg/day from the 7th to the 10th day before parturition produces a concentration in neonatal blood of 2–4 $\mu\text{g/ml}$, which gradually decreases over the following 12 days [2].

Indomethacin is not advised during pregnancy [3,4,5,6,7] because, as has been established experimentally in sheep [8], inhibition of prostaglandin biosynthesis may reduce blood flow in the pregnant uterus. It has subsequently been shown that indomethacin does not produce uterine vasoconstriction [9].

On the basis of numerous experimental and clinical investigations carried out recently, the importance of prostaglandin in determining uterine contractions and the efficacy of indomethacin in inhibiting these *in vitro* [10] and *in vivo* in the pregnant rat uterus [11,12], in the hamster [13], and in primates [14], has been established. Indomethacin has been used either alone or in association with β -mimetic drugs in the therapy of threatened premature birth [15,16,17,18, 19, 20, 21, 22, 23, 24, 25, 41, 42]. Some of these authors do not refer to maternal, foetal, or neonatal complications, while others [17, 21, 22] report that there is a significant percentage (11 cases out of 46) who present with neonatal complications which may be serious. These consist of a persistent foetal circulation syndrome with cyanosis, tachypnoea, cardiomegaly, acidosis, and hypoxaemia, which appears immediately after birth and which persists for several hours or even days. This is due to the reduced calibre of the pulmonary arterial vessels [26] and the failure of the duct of Botallo to close [43].

In the vascular walls, the prostaglandin system represents an important mechanism of regulation of muscle tone, and thus of distribution of regional blood flow. Prostaglandin $\text{F}_2\alpha$ causes vasoconstriction of the arterial ducts independent of the partial pressure of oxygen. The prostaglandin E series lowers systemic arterial pressure and resistance to pulmonary perfusion, relaxes the arterial duct in conditions of hypoxia, relaxes bronchial muscle, causes umbilical vessels to contract independently of the partial pressure of oxygen, and re-opens the arterial duct in the well-oxygenated neonate.

Indomethacin administered during pregnancy produces a marked constriction in the sheep, with a virtual closure of the arterial duct *in utero*. In the rat, rabbit, and goat, administration of indomethacin also contracts the foetal arterial duct. Neonates present with a persistent cyanosis which compromises

postnatal lactation and may seriously disturb cardiac function as a result of increased pulmonary resistance. However, the tocolytic effect of indomethacin is undoubtedly positive, particularly in cases of intolerance to the β -mimetics. Indomethacin reduces neonatal renal function in the human [27] and dog [28].

A case of phocomelia and penile agenesis has been reported in the literature in a neonate whose mother had taken 75 mg/day of indomethacin for 4 days during the 10th week of gestation. There were no other malformation [29].

Indomethacin passes into breast milk and may cause convulsions in the infant [30].

In laboratory animals, indomethacin interfered with implantation of the ovum, and was embryofoetotoxic but not teratogenic. It prolonged the duration of pregnancy and parturition.

In the mouse, indomethacin, according to some workers [31], had no harmful effects on the reproductive cycle or on foetal development. Others reported that it interfered with implantation of the fertilized ovum [32] and was embryofoetotoxic [33, 34]. Subcutaneous doses of 150 μ g/day from the 1st to the 4th day of pregnancy or as a single dose of 224 μ g on the 2nd day of pregnancy hindered implantation of the fertilized ovum, probably blocking tubule motility, which is prostaglandin-dependent. This effect was counteracted by progesterone and by prostaglandins E_2 and $F_2\alpha$ [32]. Doses of 15 mg/kg from the 8th to the 10th or from the 13th to the 15th day of pregnancy caused 17% and 32% respectively of foetal resorptions [34].

In the rat, indomethacin was embryofoetotoxic [34, 35] and modified the duration of pregnancy and parturition [11, 12, 36, 37]. Injected intra-amniotically at a dose of 50 μ g on the 15th day of pregnancy, indomethacin produced a significant increase in foetal resorptions [34]. Intramuscular doses of 4 mg/kg from the 18th to the 20th day of pregnancy caused necrosis of the neurons of the foetal central nervous system [35]. Oral doses of 0.05–0.1–0.5–1 mg/kg twice a day from the 18th day of pregnancy until parturition prolonged the duration of gestation and of parturition at the two higher doses; postnatal mortality was increased only at the highest dose [36]. An oral dose of 1 mg twice daily from the 18th day of pregnancy until parturition did not prolong the duration of pregnancy [37]. At the end of pregnancy (8 or 12 hours before parturition) a single dose of 15 mg/kg given orally caused a notable contraction of the arterial duct in the neonate, with cyanosis and respiratory distress for at least 30 minutes [38].

In the rabbit, indomethacin did not produce the same effects as in other rodents [36]. Oral doses of 0.05–0.1–0.5–1 mg/kg twice daily after the 28th day of pregnancy until parturition shortened the duration of pregnancy, although it did not affect the duration of parturition or postnatal mortality [36]. In the hamster, indomethacin prolonged the duration of pregnancy [13]. In the sheep, indomethacin administered during pregnancy caused a notable contraction of the foetal arterial duct, resulting in a change from a low to a high concentration of

oxygen [39]. In the goat, the effects of indomethacin administered during pregnancy were analogous to those in the sheep [40]. In the Rhesus monkey, indomethacin prolonged the duration of pregnancy [14].

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Sulindac

Clinoril,

(Z)-5-fluoro-2-methyl-1-(*p*-methylsulphonylphenyl-methylene)-1*H*-indene-3-acetic acid (MW 356.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Sulindac is an antipyretic, anti-inflammatory, and analgesic drug, with an arylcarboxylic acid structure. It is rapidly absorbed from the digestive tract, and partly metabolized to a sulphide derivative, which represents the active metabolite and is responsible for the anti-inflammatory action. The unchanged drug and its metabolites bind strongly to plasma proteins, thus producing a prolonged pharmacological effect. Elimination occurs mainly through the bile. The side effects of sulindac are analogous to those of similar drugs, and include gastrointestinal disturbances, vertigo, cephalia, perspiration, and skin reactions.

Although no harmful effects have been reported in the mother or the foetus, the manufacturers advise against the use of sulindac in pregnancy and during lactation, since its safety has not been established [1]. It should be noted that sulindac, like other drugs with antiprostaglandin activity, may interfere with uterine and foetal prostaglandin-dependent processes if administered chronically in pregnancy (see indomethacin, page 211).

In the rat, sulindac did not affect fertility, reproduction, or survival of the neonates. No embryofoetotoxic, teratogenic, or mutagenic effects were observed [2].

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Naproxen

Naprosyn, (+)-6-methoxy- α -methyl-2-naphthalene acetic acid (MW 230.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Naproxen is an arylcarboxylic acid derivative with antipyretic and anti-inflammatory actions, analogous to those of indomethacin, but with less marked analgesic and antiprostaglandin effects. It is rapidly and completely absorbed following oral or rectal administration, binds strongly to plasma proteins to the extent of 97.6–99.6%, depending on the concentration, and has a plasma half life of about 14 hours. It is partially demethylated and totally excreted in the urine in the free form or as a glucuronide. Because of its high affinity for albumin, naproxen interacts with drugs which are also bound to this protein, thus increasing the amount of free drug in circulation and its bio-availability. In particular, it causes signs of overdosage if administered with the sulphonylureas (oral antidiabetics), the hydantoins, and the coumarins (oral anticoagulants). The side effects of naproxen are similar to those of related drugs, and include skin rashes, thrombocytopenia, prolongation of coagulation time by inhibition of platelet aggregation, gastrointestinal irritation, gastrointestinal haemorrhage, cephalia, vertigo, and visual disturbances.

Naproxen crosses the placental barrier 20–30 minutes after oral administration [1]. It reduces the sensitivity of the uterus to oxytocin during pregnancy, and tends to inhibit the course of abortion induced by means of intra-amniotic hypertonic saline solution, because it inhibits cyclo-oxygenase [2]. A similar effect presumably occurs when the drug is administered during labour, so that its use has been proposed in threatened premature labour, by analogy with experimental results obtained in the rat [5]. Since naproxen crosses the placental barrier, it can increase free bilirubin and facilitate the appearance of neonatal jaundice [1].

Naproxen passes into breast milk, reaching a concentration 100 times less than that in the plasma.

In the rat, mouse, and rabbit, naproxen was not teratogenic [4, 6, 7], and when administered during labour it did not affect development [3, 5]. In the rat, oral doses of 2–10–20 mg/kg from the 6th to the 15th day of pregnancy were not teratogenic [4]. In the mouse and rat, oral doses of 20 mg/kg/day for 6 days half way through gestation had no serious side effects [7]. In the rat, doses of 5–15 mg/kg beginning 3 days before the end of pregnancy prolonged the duration of pregnancy in 98% of animals, and 88% of the foetuses were not delivered [5]. In the rabbit, oral doses of 2–10–20 mg/kg from the 6th to the 18th day of pregnancy were not teratogenic [6].

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Diclofenac

Voltarol, *o*-((2,6-dichlorophenyl)amino)phenylacetic acid (MW 296.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Diclofenac is an analgesic-antipyretic-anti-inflammatory drug with a phenylalkanoic acid structure. Like other similar drugs, it causes hepato-nephrotoxicity and cutaneous gastrointestinal effects.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, some authors advise against the use of diclofenac in the third trimester, although they give no reason for their recommendation [1]. Chronic administration in pregnancy may affect prostaglandin-dependent mechanisms in the uterus and the foetus (see indomethacin, page 211).

In the mouse and rat, diclofenac was neither embryofoetotoxic nor teratogenic [2]. In the mouse, oral doses of 1–4 mg/kg/day from the 7th to the 12th day of pregnancy were without harmful effects on the foetus or the pregnant animal [2]. In the rat, similar doses from the 9th to the 14th day of pregnancy were similarly without side effects in the foetus or the pregnant animal [2].

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Indoprofen or isindone

Flosint,

α -(4-(2-isindoliny1-1-one)phenyl)propionic acid (MW 281.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Indoprofen is an analgesic-antipyretic-anti-inflammatory drug derived from

phenylalkanoic acid, and is used mainly in the treatment of pain. Its principal side effects are nausea and vomiting.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we think that indoprofen should be used with care in pregnancy, because of its effect on prostaglandin metabolism (see indomethacin, page 211).

In the rat and hamster, indoprofen was not teratogenic [1, 2, 3]. In some investigations, an embryofoetotoxic action was reported [2]. In the rat, oral doses of 6–12–24 mg/kg/day from the 6th to the 15th day of pregnancy had toxic effects on the mother at higher doses, but were not embryofoetotoxic or teratogenic [1]. In the hamster, oral doses of 16–32–64 mg/kg/day given before and during pregnancy were embryofoetotoxic but not teratogenic [2]. However, other authors [3], using the same doses and the same method of administration, found no harmful effects.

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Fentizac

4-(*p*-chlorophenyl)-2-phenyl-5-thiazolyl acetic acid (MW 329.8)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Fentizac is a non-steroid drug with anti-inflammatory, analgesic, and antipyretic actions.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, chronic administration of fentizac in pregnancy should be avoided, because of its antiprostaglandin effect (see indomethacin, page 000).

In laboratory animals, at doses considerably higher than therapeutic, fentizac was not teratogenic and did not affect the viability or the development of the neonate at term [1].

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6. MISCELLANEOUS ANTIRHEUMATICS

Benzidamin(1-benzyl-3-(3-dimethylamino)propoxy)-1*H*-indazole (MW 309.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Benzidamin has anti-inflammatory, analgesic, and antipyretic actions.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we believe that benzidamin should be used with care in pregnancy because of insufficient evidence for its safety.

In the mouse, rat, and rabbit, benzidamin had no embryofoetotoxic or teratogenic effects [1,2]. In the mouse, oral doses of 40–200 mg/kg and 20–100 mg/kg given subcutaneously from the 7th to the 12th day of pregnancy were neither embryofoetotoxic or teratogenic [1]. In the rat, oral doses of 40–200 mg/kg and 30–150 mg/kg given subcutaneously from the 9th to the 14th day of pregnancy were not teratogenic [1]. In the rabbit, doses of 208 mg/kg administered throughout pregnancy did not significantly increase foetal resorptions or malformations. Doses of 200 mg/kg from the 7th to the 17th day of pregnancy were likewise not teratogenic, and did not affect the incidence of foetal resorptions [2].

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*Diphthalone*phthalazino-(2,3-*b*)phthalazine-5(14*H*)-12(7*H*)-dione (MW 264.28)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Diphthalone is a phthlazine derivative with an anti-inflammatory action which is superior to that of acetylsalicylic acid, but inferior to that of indomethacin. Its principal characteristics are that it does not cause gastrointestinal irritation and is not hepatotoxic. Since it does not have a steroid structure, it does not affect the endocrine system. The analgesic, antipyretic, and sedative effects of diphthalone are weak, but among the non-steroidal anti-inflammatory drugs, it occupies an important position.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we believe that diphthalone should be used with care in pregnancy because there is insufficient evidence of its safety.

In the rat, diphthalone was neither embryofoetotoxic nor teratogenic [1]. Administration of doses of 500–1000 mg/kg showed no evidence of uterotropic or anti-oestrogenic activity. At doses of 100 mg/kg/day for 5 days, diphthalone had an antiprogesterone effect, inhibiting uterine growth and endometrial glandular development in the uterus sensitized by oestrogens. Administration of 50–100–200 mg/kg orally for 5 days did not affect transport of the ovum or its implantation. Oral administration of 200 mg/kg for 5 days after implantation of the ovum did not interrupt the pregnancy or alter the number of foetuses which had developed normally when examined on the 16th day of gestation [1]. The isolated rat uterus retained its contractility [2] in the presence of high concentrations of diphthalone (10^{-4} g/ml).

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Tolmetin sodium

Tolmetin, sodium

(1-methyl-5-*p*-toluyl-pyrrol-2-yl)acetate dihydrate (MW 315.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Tolmetin is an anti-inflammatory, derived from pyrrole acetic acid, and is used in the treatment of rheumatoid arthritis. It has slight analgesic activity and toxicity, which is manifested in the digestive tract (nausea, vomiting, diarrhoea, haemorrhage), in renal function, and in the central nervous system (buzzing,

cephalia, vertigo, depression). Tolmetin may cause fluid retention, hypertension, urticaria, and prolongation of bleeding time, as a result of interference with platelet function. The drug is almost completely metabolized, and binds strongly to plasma proteins.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we believe that tolmetin should be used with care in pregnancy because there is insufficient evidence of its safety.

In the rat and rabbit, tolmetin was neither embryofoetotoxic nor teratogenic [1]. Administration of the drug at doses up to five times therapeutic at various stages of pregnancy were not teratogenic [1].

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Methiazinic acid

10-methyl-phenothiazine-2-yl-acetic acid (MW 271.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Methiazinic acid has marked anti-inflammatory activity, with slight analgesic and antipyretic properties.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we believe that methiazinic acid should be used with care in pregnancy, because there is insufficient evidence of its safety.

In the mouse, rat, and rabbit, administration of methiazinic acid in pregnancy was embryofoetotoxic only at high doses [1]. In the mouse, administration of the drug orally at doses of 10–30–60 mg/kg/day from the 4th to the 15th day of pregnancy had no harmful effects, and did not affect weight gain in the neonates [1]. In the rat, oral administration of similar doses from the 5th to the 15th day of pregnancy caused no foetal side effects [1]. In the rabbit, oral administration of the drug at doses of 10–30–60 mg/kg/day from the 6th to the 16th day of gestation had no teratogenic effects, but some degree of foetal resorption was observed at high doses [1].

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* * * * *

Feniramidol

1-phenyl-2-(pyridin-2-ylamino)ethanol hydrochloride (MW 250.7)

Feniramidol is an analgesic and is a weak hypocholesterolaemic. It is used in myalgia.

Aminopropylone

phenylbutazone derivative of

1-phenyl-2,3-dimethyl-4- α -dimethyl-amino-propionylamido-5-pyrazolone (MW 302.4)

Niapirin

1-phenyl-2,3-dimethyl-4-(*N*-nicotinamidomethyl-*N*-isopropyl) 1-amino-5-pyrazolone (MW 379.46)

Dinoranodipyrin

1-phenyl-2,3-dimethyl-4-salicylamido-pyrazolone-5 (MW 323.35)

Chlortenoxazin

2-(β -chloroethyl)-2,3-dihydro-4-oxo-(benzo-1,3-oxazine) (MW 211.65)

Chlortenoxazin is an analgesic and anti-inflammatory drug which is used in rheumatic myoarthralgias.

Oxycincophen

3-hydroxy-2-phenyl-cinchoninic acid (MW 265.26)

Oxycincophen is an antirheumatic, antipyretic, and analgesic drug which has some hepatic toxicity and an irritant effect on the gastrointestinal tract.

Isophthalolic acid

4-hydroxy-isophthalic acid (MW 182.14)

Indosamide or glucamethacin

glucosamide of

(*N*-*p*-chlorobenzoyl-2-methyl-5-methoxy)indole-3-acetic acid monohydrate (MW 536.99)

Sulphenazone

(2,3-dimethyl-1-phenyl-5-oxo-3-pyrazolin-4-yl)-(*p*-(6-methoxy-3-pyridazinyl-sulphamoyl)-anilino)methansulphonate sodium (MW 582.6)

Fenbutanidol

2-phenyl-3-hydroxy-4-*n*-butyl-5-pyrazolinonate of
2- β -hydroxyphenethyl-amino-pyridine (MW 446.56)

Benzopiperilone

1-(*N*-methyl-4-piperidyl)-3-phenyl-4-benzyl-5-pyrazolone (MW 346.46)

We have been unable to find any information on clinical or research studies on these drugs, either in the literature or from the manufacturers. However, even although there were no reports on harmful effects, we believe that in the absence of sufficient evidence of safety, the use of these drugs in pregnancy or in women of childbearing age who are likely to conceive should be avoided.

Prostaglandin F₂ α tromethamine or Dinoprost tromethamine

(*Z*)-7-((1*R*, 2*R*, 3*R*, 5*S*)-3, 5-dihydroxy-2-((*E*)-(3*S*)-3-hydroxy-oct-1-enyl) cyclopentyl)hept-5-enoic acid linked with
2-amino-2-(hydroxymethyl)-propane-1, 3-diol (MW 475.6)

The prostaglandins are unsaturated fatty acids containing 20 atoms of carbon. They are present in all tissues. They are derived from essential fatty acids. The structures of the prostaglandins are derived from the hypothetical prostanoid acid, which is formed from a cyclopentane ring with two aliphatic side chains and a terminal carboxylic acid group. The configuration of the ring and its substituents indicates the series to which the various prostaglandins belong. The thromboxanes also form part of the prostaglandin system but do not have the prostanoid acid structure. They are, however, derived from arachidonic acid. Prostacyclin or PGX has a prostanoid acid structure, but is at the same time an endoperoxide, as is thromboxane A₂.

Prostaglandins of the E series have a vasodilator action and cause contraction of nonvascular smooth muscle. Prostaglandins of the F series are able to contract nonvascular smooth muscle. Prostaglandins of the A series have vasoactive properties analogous to those of the E series. Thromboxane A₂ is a potent platelet aggregator. Prostacyclin inhibits platelet aggregation.

Biosynthesis of the various components of the prostaglandin system starts from the polyunsaturated fatty acids with 20 carbon atoms, which are usually incorporated in the phospholipids of all cellular membranes and are released by the action of the enzyme phospholipase A₂. The components of the prostaglandin system are not stored but are rapidly released after biosynthesis

and equally rapidly metabolized to inactive substances. In normal conditions, they are present in small quantities as the amounts of free polyunsaturated fatty acids which constitute their potential precursors are also present in very small quantities. Degradation of prostaglandins occurs mainly in the lungs, the liver, the kidneys, and the placenta with a rapidity that prevents them from being considered as circulating hormones, and they therefore act only near the point of synthesis.

The physiological role of the prostaglandin-like substances seems to depend on their regulation of many processes such as inflammation, fever, intravascular coagulation, regional blood flow, neurotransmission, reproductive function, endocrine equilibrium, arterial pressure, and gastric secretion.

Therapeutically, the prostaglandins are used as potent oxytocics, and they participate in causing an active, spontaneous type of initiation of labour. It is believed that the prostaglandins, in addition to the post-hypophysial hormones, may be responsible for the initiation of labour. Uterine distension can stimulate the production of oxytocin by a reflex route and, at the same time, cause the synthesis of prostaglandins in the myometrium. Uterine contractions may cause an increase in uterine prostaglandins, which increase the response to oxytocin. The synchronization of these events sets in motion a real labour at low plasma concentrations of oxytocin.

Prostaglandin $F_2\alpha$ may be administered intravenously, intra-amniotically and extra-amniotically. The intravenous route is indicated in the induction of labour near to term, when there has been intra-uterine death of the foetus, in induction of abortion during the second trimester, and to obtain the expulsion of an hydatid cyst, particularly after suitable chemotherapy. Intravenous administration is often accompanied by notable side effects such as nausea, vomiting, diarrhoea, fever, leucocytosis, cephalia, perspiration, and hot flushes. In the induction of abortion, the extra-amniotic route is used, and in the second trimester, the intra-amniotic route, which produces less marked side effects.

Prostaglandin $F_2\alpha$ is contra-indicated in patients who have inflammation, asthma, glaucoma, or any particular hypersensitivity.

Prostaglandin $F_2\alpha$ and its derivatives, as previously mentioned, are used to produce abortion in the second trimester of pregnancy, and there are no side effects in the pregnant woman [6,7,8,9,10,22]. After intra-amniotic injection of 15-Me-PGF $_2\alpha$, at doses of 2.5 or 5 mg in 20 pregnant women, between the 13th and the 22nd week of pregnancy, expulsion of the foetus occurred in a short time in all the patients [6].

Prostaglandins $F_2\alpha$ and E_2 are used for the induction of labour [12,13,14,15,16] without side effects in the foetus [11,17,18]. In a study on 60 pregnant women at term, and 12 before term, PGF $_2\alpha$ did not produce toxic effects in the foetus [17]. In another study, the absence was stressed of pathological manifestations in the foetus, after the use of the drug as an inducer of parturition [11]. The same authors maintain that the use of the prostaglandins is

potentially dangerous in that it may cause uncoordinated uterine contractions [19, 20] and uterine hypotonia [21].

In the mouse, rat, and rabbit, $\text{PGF}_2\alpha$, when administered at the beginning of gestation, impeded implantation. In the more advanced stages of gestation it had no harmful effects on the mother but a weak teratogenic and foetotoxic action, as well as an abortive or ecobolic action because of its selective activity on the uterus.

In the mouse, intraperitoneal administration of $\text{PGF}_2\alpha$ at doses of 0.05–0.1–0.25 mg/kg from the 7th to the 12th day of gestation had no appreciable side effects in the foetus [1]. $\text{PGF}_2\alpha$ had no direct effects *in vitro* on the mouse embryo prior to implantation [2].

In the rat, administration intravenously of $\text{PGF}_2\alpha$ at doses of 0.1–1–1.5–2 mg/kg from the 9th to the 14th day of pregnancy significantly increased the number of foetal resorptions and reduced foetal growth at all but the lowest dose. At doses of 2 mg/kg, $\text{PGF}_2\alpha$ significantly increased the number of malformed foetuses [1]. $\text{PGF}_2\alpha$ administered as a single dose of 1 mg/kg intravenously on the 19th day of pregnancy did not cause toxic effects in the pregnant animal, but consistently caused abortion of the foetus [3].

In the rabbit, administration of $\text{PGF}_2\alpha$ prior to implantation of the blastocyst altered the development of the corpus luteum and of the embryo, and after implantation caused complete degeneration of the embryo [4]. Prostaglandins E_1 , E_2 , and $\text{F}_2\alpha$ did not affect the development of blastocysts cultured *in vitro* [5].

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Part 8

Drugs with a metabolic action

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1. AMINO ACIDS AND NUTRITIONAL SUBSTANCES

Among the amino acids and polypeptides, and other nutritional substances, the following are discussed in this chapter:

	Recommendation	Page
Glycine	NC	229
Creatinol phosphate	NC	230
Phosphocreatinine	NC	230
Fructose-1, 6-diphosphate	NC	230
Taurine	NC	232
Lecithin	NC	232
Carnitine	NC	233
Ethyl glutamate	NC	233
Potassium aspartate	NC	234
Aspartic acid	NC	234
Arginine	NC	234
Asparagine	NC	235
Serine phosphate	NC	235
Saccharomyces boulardii	NC	236
Choline bitartrate	NC	236
Choline citrate	NC	236
Choline phytate	NC	236
Phosphorylcholine chloride	NC	236
Choline dehydrocholate	NC	236
Cyticholine	NC	237
Methionine	NC	238
Adenosyl methionine	NC	238
Inositol	NC	239
β -mercaptoethylamine		
hydrochloride	NC	239
Acetylglutamide	NC	240
Laevoglutamide	NC	240
Sodium bromohistidinate	NC	240
Histidine monohydrochloride	NC	240
Aprotinin	NC	241
Gangliosides	NC	242
Brominated hydrolyzed protein	P (P during lactation)	242
Angiotensinamide	P	243

The majority of the above drugs are not contra-indicated in pregnancy, since many of them form constituents of the organism and others are essential foodstuffs. The multiplicity of substances included in this group is such that it is impossible to summarize their characteristics, and thus each one is dealt with separately.

We believe that there is insufficient evidence of safety to accurately assess the following drugs in pregnancy: antihæmorrhagic factor, laevocystine, ethanolamine phosphate (see page 244).

Glycine

Titralac, Paynocil, amino-acetic acid (MW 75.07)

Not contra-indicated in pregnancy.

Glycine is the simplest aliphatic monoamino-monocarboxylic amino acid, and is synthesized from serine, via ethanolamine, starting with tetrahydrofolic acid. This last reaction is reversible and allows the transformation of glycine into serine and thence into pyruvate. It is believed that glycine has an inhibitory action in the central nervous system, analogous to that of GABA (γ -aminobutyric acid). It has been established that glycine is used for the hepatic biosynthesis of glycocholic acid (biliary acid), for the formation of the purine ring, and of creatinine, important constituents of muscle cells. Glycine is thus used in the treatment of the myopathies.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of glycine in pregnancy in laboratory animals. Glycine was found to be teratogenic in the chick embryo [1, 2, 3]. Injection of 0.15–0.25 ml of a solution of glycine in 1280 eggs caused the death in 9 days of 1216 embryos, while of the 64 surviving ones, 59 had malformations. There was also incomplete growth, extraversion of the viscera, exophthalmos, alterations of the legs and of the beak [1]. Afterwards, it was seen that vitamin B₁₂ and folic acid protected against the teratogenic action of glycine, while aminopterin (a folic acid antagonist) increased the frequency of malformations [2, 3].

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Creatinol phosphate

monosodium salt of *N*-methyl-*N*- β -*N*-hydroxyethylguanidine-*O*-phosphate (MW 197.09)

Not contra-indicated in pregnancy.

Phosphate creatinol is a constituent of muscle tissue, which serves as a donor of high-energy phosphate radicals. It is used as a myocardiotropic agent.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat and dog, creatinol had no embryofoetotoxic or teratogenic effects [1]. In the rat, oral doses of 100 mg/kg throughout pregnancy were without harmful effects [1]. In the dog, similar doses were innocuous [1].

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Phosphocreatinine

2-imino-1-methyl-4-oxo-imidazolidine-3-phosphoric acid (MW 193.1)

Not contra-indicated in pregnancy.

Phosphocreatinine, a donor of high-energy radicals, is commonly used in myocardiotropic therapy (see creatinol phosphate, see above).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of phosphocreatinine in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta Midy - Milano.

Fructose-1, 6-diphosphate

(MW 340.2)

Not contra-indicated in pregnancy.

Fructose-1,6-diphosphate is an intermediate metabolite of anaerobic glycolysis, and is derived by phosphorylation of fructose-6-phosphate by the action of ATP with the aid of phosphofructokinase. This enzyme represents a controlling step in the glycolysis chain, since it is stimulated by AMP and ADP, and inhibited by ATP and by citrate. Fructose-1,6-diphosphate is split by an aldolase, with formation of two triose phosphates.

Fructose-1,6-diphosphate may be used for gluconeogenesis after conversion to fructose-6-phosphate. The synthesis of the enzyme 1,6-phosphate-1-phosphatase is stimulated by cortisol and depressed by insulin.

Fructose-1,6-diphosphate is immediately available, because it is already completely phosphorylated, and is thus a high-energy substrate. In addition, it exerts an allosteric regulatory action on the activity of the enzyme involved in the biosynthesis of fatty acids in the liver and on pyruvate kinase. Its therapeutic value is thus easily understandable. It is used in diabetes, in some nervous and muscular complaints, in hepatology, and in cardiology.

With regard to the use of fructose-1,6-diphosphate in obstetrics, apart from a few interesting experimental investigations, it is used to increase uterine contractions, in the absence of phosphorylated glucides secondary to foetal hypoxia, and for nutrition of the foetus during pregnancy. Experimentally, fructose-1,6-diphosphate *in vitro* increases basal tone of human uterine smooth muscle at the end of pregnancy [1], increases the frequency and the amplitude of the contractions, and potentiates muscle responses to oxytocic stimulation [2] in the horn of the isolated guinea-pig uterus [3]. It also potentiates the incorporation of amino acids into the placenta *in vitro* [4].

Fructose-1,6-diphosphate has been shown to be useful in stimulating uterine contractions in cases of secondary inertia [5, 6]. Numerous investigations have shown its efficacy in foetal distress [7, 8, 9, 10, 11, 12, 13, 18]. It is useful in toxæmia, improving the general condition of the pregnant woman and the foetus [14]. In placental insufficiency, fructose-1,6-diphosphate is lacking in the placental tissue [15, 16], and in some cases its administration causes an improvement in the concentration of placental protein hormones (HCG, HPL) in the maternal plasma [17]. There are no contra-indications to the use of this drug in pregnancy or labour.

No experimental studies have been described on the use of fructose-1,6-diphosphate in pregnancy in laboratory animals.

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Taurine

2-amino-ethansulphonic acid (MW 111.06)

Not contra-indicated in pregnancy.

Taurine is a sulphonated amino acid, and is present in the free form or combined with bile acids (taurocholate). It is derived by oxidation and decarboxylation of cysteine in the liver. Taurine is not incorporated into the proteins and represents an oxidation product in the metabolism of sulphonated amino acids. It is used in diseases resulting from insufficiency of tissue oxygenation.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, treatment with high doses of taurine (280 mg/kg) produced no embryofetotoxic or teratogenic effects [1].

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- [1] Comunicazione personale della Ditta Falorni - Firenze.

Lecithin

phosphatidyl choline (MW 760.0)

Not contra-indicated in pregnancy.

Lecithin is a phospholipid which is synthesized by the following four metabolic pathways:

- (1) starting from active choline (CDP choline) and from diacyl-glycerol;
- (2) by metabolism of phosphatidyl-ethanolamine by means of SAM (*S*-adenosylmethionine);
- (3) by acylation of lysolecithin;
- (4) by condensation of two molecules of lysolecithin, of which one functions as a donor of fatty acids and the other as acceptor.

Lecithin is catabolized to glycerol-phosphoryl-choline by means of two different phospholipases or lecithinases. A1 removes the acyl group in position 1, and A2 removes the other. Subsequently lysophospholipase removes the last acyl group, and glyceryl-phosphoryl-choline is formed. The activation of phospholipase A2 is the first step in the biosynthesis of the prostaglandins.

Lecithin is the principal constituent of cell membranes and of myelin.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2].

No experimental studies have been described on the use of lecithin in pregnancy in laboratory animals.

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Carnitine

trimethylbetaine of 3-amino-3-oxybutyric acid (MW 161.2)

Not contra-indicated in pregnancy.

Carnitine is not a vitamin, in that no pathological manifestations of deficiency have been described. However, from the clinical point of view, it has been shown to possess some interesting therapeutic actions. It stimulates digestive secretion, favours intestinal absorption, reduces protein catabolism following starvation, hypothyroidism or from cortisone, and favours fixation of calcium in bones. Because of its structural similarity to choline, it was thought that carnitine would have a lipotropic action, but this has not been confirmed.

Carnitine regulates lipid metabolism, facilitating the penetration of fatty acids into the cells. In the presence of acetate, ATP, and coenzyme A, it is transformed to acetylcarnitine, which provides the necessary energy for initiating oxidation of the fatty acids [1] in the mitochondria. Carnitine stimulates the formation and the oxidative utilization of ketone bodies [2] and activates gluconeogenesis from lipids.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [5].

In the chick embryo, carnitine stimulated bone growth, but no teratogenic effects were reported [3, 4].

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Ethyl glutamate

L-glutamate acid γ -ethyl ester (MW 161.17)

Not contra-indicated in pregnancy.

Glutamic acid is a molecule of considerable biological importance. It has a depolarizing action on neuronal membranes and thus could be a transmitter in the central nervous system. It is one of the constituents of folic acid (pteroylglutamic acid) and thus in metabolism of the monocarbon unit. It can function in ammonia fixation, transforming the latter into glutamine. Because of this property, ethyl glutamate can be used in hyperammonaemia resulting from hepatic insufficiency and in the correlated neurotoxic manifestations.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy [1].

In laboratory animals, studies by the manufacturers have excluded any embryofetotoxic or teratogenic effects [1].

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- [1] Comunicazione personale della Ditta Maggioni - Milano.

Potassium aspartate

(MW 209.3)

Aspartic acid

(MW 133.1)

Not contra-indicated in pregnancy.

Potassium aspartate has a dual action. It can correct depletion of potassium (without the addition of chloride ions, which may be undesirable), and hyperammonaemia, by acting as a nitrogen acceptor.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of potassium aspartate in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Wyeth - Aprilia.

Arginine

1-amino-4-guanidinovaleric acid (MW 174.2)

Not contra-indicated in pregnancy.

Arginine is important in one step of the Krebs-Hanseleit cycle, which transforms ammonia into urea, a less toxic substance, which is readily eliminated in the urine. Often there is a metabolic block which does not allow the regeneration of arginine. However, administration of this metabolite may be useful therapeutically in hyperammonaemia.

Slight but progressive hyperammonaemia may be observed in hyperemesis gravidarum [1]. Arginine, as the glucose-1-phosphate salt, has been used in toxemia with the object of detoxication, producing an improvement in some aspects of renal function [2, 3, 4, 5] without the appearance of embryofetotoxic or teratogenic effects.

No experimental studies have been described on the use of arginine in pregnancy in laboratory animals.

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Asparagine

arginine *N*-acetyl-asperginate (MW 132.12)

Not contra-indicated in pregnancy.

Asparagine the amide of aspartic acid, acts as an acceptor of ammonia and of glutamine. Aspartic acid is considered as an excitatory neurotransmitter in the central nervous system. Arginine, the final product of urogenesis, may be transformed into glutamic acid, another neurotransmitter, with a similar action. Acetylasparginate of arginine is used as a physiological mental stimulant.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of asparagine in pregnancy in laboratory animals.

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- [1] Comunicazione personale della Ditta Lirca - Milano.

Serine phosphate

serine acid phosphate (MW 185.08)

Not contra-indicated in pregnancy.

Serine phosphate is a non-essential glucogenic hydroxy-amino acid which is widely distributed in nature. It is synthesized by two distinct routes, starting from phosphoglyceric acid and from phosphoglyceraldehyde, an intermediate product in glycolysis and in the pentose phosphate pathway. Serine may be transformed into ethanolamine, choline, betaine, glycine, cysteine, sarcosine, sphingosine, pyruvate, and then glucose. Serine forms part of the phosphatides (phosphatidyl-serine) and of the enzyme cholesterol esterase. It is also important in the synthesis of glycogen and acts as a covalent link which unites protein to polysaccharide residues (glycoproteins). It is present in the principal phosphoproteins (e.g., in caseine) in the form of a phosphoric ester (serine phosphate). Serine phosphate is used in therapy to 'reconstitute the nervous system'.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of serine phosphate in pregnancy in laboratory animals.

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- [1] Comunicazione personale della Ditta S.I.T. - Meda Lomellina (Pavia).

Saccharomyces boulardii

Saccharomyces boulardii 17 lyophylized

Not contra-indicated in pregnancy.

Saccharomyces boulardii, a species of yeast, has the characteristics of an antibiotic-resistant substance. Its administration, therefore, represents a way of giving B vitamins in the 'nascent' state, which is useful during or after treatment with antibiotics which destroy intestinal flora. When intestinal colonization occurs, this species may antagonize pathogenic flora, and give rise to the production of ammonia, thus aggravating hyperammonaemia in hepatic failure.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1]. They also advise that *Saccharomyces* may safely be used in the neonate.

No experimental studies have been described on the use of *Saccharomyces boulardii* in pregnancy in laboratory animals.

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Choline bitartrate

(MW 254.29)

Choline citrate

(MW 296.33)

Choline phytate

(MW 764.27)

Phosphorylcholine chloride

(MW 219.65)

Choline dehydrocholate

(MW 506.7)

Not contra-indicated in pregnancy.

Choline is a biogenic amine derived from serine and from methionine (via ethanolamine), or by hydrolysis of acetylcholine, the neurotransmitter in the cholinergic synapse. It is also a constituent of phosphatidylcholine or lecithin, a phosphoglyceride which has a very important role as a structural component of the cellular membrane.

Biosynthesis of choline is based upon availability of precursor amino acids (methionine and serine) and of methyl groups, supplied directly by activated methionine (*S*-adenosyl-methionine, SAM) or indirectly from the monocarbon unit supplied by folates.

Choline is rapidly oxidized to betaine by the choline oxidase system, and only then can it act as a donor of methyl groups in processes of transmethylation. It is also important for the biosynthesis of lecithin and thus gives rise to the so-called 'lipotropic' action, which results in the prevention of experimental hepatic steatosis. In fact, biosynthesis and turnover of phospholipids are accelerated by administration of choline. An analogous lipotropic action is also produced by methionine and by inositol. Administration of choline by any route does not noticeably increase blood levels, because it is immediately transferred to tissues and oxidized in the liver. High doses of choline give rise to a pharmacological action similar to that of acetylcholine (peripheral vasodilatation, hypotension, uterine stimulation, etc.). Choline has been used therapeutically in hepatocellular lesions. Its clinical efficacy has not, however, been definitely established.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, with choline bitartrate [1,2,3] and for phosphorylcholine [1,2,4]. Phosphorylcholine chloride, used in the treatment of toxæmia in the third trimester, caused no side effects in the foetus [4].

No experimental studies have been described on the use of choline in pregnancy in laboratory animals.

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Cyticholine

cytidine-diphosphocholine (MW 488.2)

Not contra-indicated in pregnancy.

Cyticholine is an 'activated' choline derived from phosphoryl-choline, which is utilized in the biosynthesis of lecithin. Many properties of cyticholine are similar to those of choline (see page 205). It is a precursor of acetylcholine in the brain, and it is used in the treatment of arteriosclerotic disease, and as a precursor of phospholipids in the prevention of neonatal respiratory syndrome [1].

Cyticholine has been used at various stages of pregnancy because of its effect on maturation of foetal lungs. There were no side effects in the mother or the foetus [1].

In the rabbit, cyticholine increased the production of surfactant in foetal lungs [2,3].

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Methionine

(MW 149.21)

Adenosyl methionine

(MW 398.45)

Not contra-indicated in pregnancy.

Methionine is an essential sulphonated amino acid which is of fundamental biological importance. It is synthesized in the organism only if a suitable source of methyl groups and homocysteine is available. The methyl groups come from betaine (and thus from dietary choline) or from 5-methyl tetrahydrofolate (from the pool of monocarbon units).

Methionine is activated by ATP to *S*-adenosyl-methionine (SAM) and enters the processes of trans-sulphuration (synthesis of cysteine, of glutathione, etc.), and of transmethylation (synthesis of choline and thus of the lecithin of cellular membranes, of acetylcholine, the neurotransmitter at cholinergic synapses, synthesis of muscle creatinine, catabolism of catecholamines, detoxicating methylation of drugs). Methionine is thus a regulator of SNC, of lipid, and of protein metabolism. It is also indispensable for the synthesis of the polyamines and for the initiating reaction in protein biosynthesis, in that the whole peptide chain always contains methionine at the *N*-terminal. Methionine may also be used to provide energy in the Krebs cycle and initiate transformation into propyl and succinyl coenzyme A.

The therapeutic use of methionine was suggested by its experimental 'lipotropic' action, but its clinical usefulness in the hepatopathies has not been confirmed. When methionine is administered it is actively retained in the organism. After intravenous administration, blood levels fall rapidly to normal, methionine being rapidly distributed to the tissues. This phenomenon has been used to measure indirectly the rate of foetal protein synthesis. Intravenous administration of selenium-methionine, a γ -emitter, causes an accumulation of amino acids in the foetal liver, which is measureable externally, and is proportional to transplacental passage of the amino acid and the rate of foetal growth [1].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2, 3, 4].

No experimental studies have been described on the use of methionine in pregnancy in laboratory animals.

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Inositol

meso-inosite (MW 180.18)

Not contra-indicated in pregnancy.

Inositol is a glucide constituent of the cerebral phospholipids (inositol-phosphatide or phosphatidylinositol), which has a 'lipotropic' action, or rather, which can protect against experimental hepatic steatosis in a similar manner to choline and methionine. Exogenous inositol is not actively metabolized, but is eliminated as such. Its therapeutic use is subject to the same misgivings as choline (see page 205).

The physiological concentration of inositol in foetal blood is greater than that in the mother, which suggests that it is synthesized in the foetus. During lactation, the need for inositol increases, because of the loss in milk secretion [1]. There have been no reports of harmful effects following the use of inositol in pregnancy [1, 2, 3, 4].

No experimental studies have been described on the use of inositol in pregnancy in laboratory animals.

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β -mercaptoethylamine hydrochloride or cysteamine or mercaptamine

(MW 112.54)

Not contra-indicated in pregnancy.

Cysteamine is a protective agent against radiation. Its mechanism of action is based on regulation of glucide metabolism, which is often affected by radiation, as a result of a shift in the ratio between reduced and oxidized glutathione, with an increase in the latter. The activating effect of glutathione on some phases of glucide metabolism has been demonstrated [1].

In toxæmia and eclampsia, there is a diminution in glutathione levels in favour of the oxidized form, with an increase in the ratio GSH/GSSG. Administration of cysteamine has been shown to return this ratio to normal [1, 2].

In the rat, cysteamine was embryofetotoxic but not teratogenic [3]. In chick embryo it was also teratogenic [4]. In the rat, cysteamine administered at a dose of 375 mg/kg for two generations caused a reduction in the number of

foetuses implanted. It also caused a retardation in weight gain in the sucklings of animals being treated [3].

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Aceglutamide

N-acetyl-L-glutamine (MW 188.8)

Laevo glutamide

L-glutamine (MW 146.15)

Not contra-indicated in pregnancy.

Glutamine, the amide of glutamic acid, represents the principal form of transport for ammonia which is formed during protein catabolism. For example, the brain, which is rich in glutamine synthetase, eliminates ammonia by incorporating it into glutamic acid, with the formation of glutamine. In the liver, ammonia is slowly released and converted to urea. Similarly, the kidneys transform glutamine into glutamic acid and ammonia, and thus prevent metabolic acidosis. Glutamine is essential for the synthesis of purine and pyrimidine nucleotides. Its antimetabolite azaserine is used as an antitlastic. Glutamine acting as a donor of ammonia is transformed into glutamic acid, which is an excitatory neurotransmitter in the central nervous system, particularly in the mentally retarded, where its administration produces an increase in intelligence quotient.

No reports have been found of harmful effects on the human foetus, the mother or the pregnancy [2], and the manufacturers concur with this view [1].

No experimental studies have been described on the use of aceglutamide in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta ISF - Milano.
- [2] *Dictionaire Vidal* - O.V.P. Ed. - Paris, 1975.

Sodium bromohistidinate

(MW 256.03)

Histidine monohydrochloride

α -amino- β -imidazoly1-propionic acid (MW 191.61)

Not contra-indicated in pregnancy.

Histidine is an amino acid which is given intramuscularly in the treatment of peptic ulcer. An oral dose of histidine has been proposed as a test to indicate lack of folate on the basis of FIGLU and of urocanic acid excreted in the urine.

Histidine has been used in pregnancy in the treatment of emesis and other gastric and duodenal disorders with no harmful effects on the foetus [1].

No experimental studies have been described on the use of histidine in pregnancy in laboratory animals.

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Aprotinin

Trasylol (MW 651.2)

Not contra-indicated in pregnancy.

Aprotinin is a polypeptide formed from 58 amino acids with three disulphide bridges, extracted from bovine lung and measured in units required to inactivate kallikrein. Aprotinin also inhibits some proteolytic enzymes, including kallidinogenase, plasmin, trypsin, chymotrypsin, lysosomal proteases, proteases in the first step of fibrinolysis, proteases which lead to the formation of kinins. It does not inhibit pepsin, aminopeptidase, or carboxypeptidase. Inactivation of the proteolytic enzymes occurs by formation of reversible bonds.

Aprotinin inhibits the initial steps in the blood coagulation process, and arrests fibrinolysis. In addition, it inactivates plasma proteases which are primers in conditions of hypoxia and cellular metabolic acidosis, and which cause the production of kinins which have powerful vasodilating properties and increase permeability. Aprotinin reduces capillary permeability and vasodilation, restores circulatory volume, and improves peripheral circulation as a result of its anti-thrombic effect. It is therefore used in the prevention and treatment of shock, acute pancreatic necrosis, haemorrhagic syndromes caused by hyperfibrinolysis, and prevention of adhesions following surgery. The polypeptide nature of this drug implies a potential risk of hypersensitivity.

Aprotinin crosses the placental barrier [1]. Administration at various stages of pregnancy has not produced embryofoetotoxic or teratogenic effects [2, 3, 4, 8, 9, 11]. Five cases were described with acute pancreatitis in pregnancy who were treated with aprotinin at doses of 250 000–1 000 000 IU intravenously. The neonates of four of the patients were normal, but in a fifth patient therapeutic abortion was required because of serious renal complications [4]. Aprotinin administered before birth did not adversely affect the mother or the foetus [7], in fact according to some studies [5] it improved the Apgar score and general condition of the infant.

In the rat, administration of 50 IU from the 19th to the 22nd day of pregnancy was neither embryofoetotoxic nor teratogenic, but prolonged the duration of pregnancy and labour [6].

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Gangliosides

Not contra-indicated in pregnancy.

Gangliosides constitute part of the cellular membranes, and possess a fundamental role in the mechanism of reception of information by the cell. This action occurs via (1) control of surface potential, (2) interaction between calcium and magnesium ions, and (3) formation of specific sites with which molecules with informational capacity combine. Gangliosides particularly stimulate the regeneration of nerve fibre function, and they are therefore used in neurological problems characterized by alterations in excitability and nerve transmission.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat and rabbit, gangliosides were neither embryofoetotoxic nor teratogenic [1]. In the rat, doses of 0.5–5–25 mg/kg administered throughout pregnancy were without harmful effects [1]. In the rabbit, doses of 0.5–1–5 mg/kg from the 6th to the 16th day of pregnancy caused no side effects on the foetus [1].

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Brominated hydrolyzed protein

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		P

To be used with care in pregnancy and during lactation.

Bromine is transported by a mixture of amino acids obtained by hydrolysis of albumin. The product is used as a sedative.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. The action of bromides on the pregnant women,

on the pregnancy, and on the neonate and the suckling should be borne in mind. Administered in this situation, bromine could be toxic, causing delirium [1]. Brominated hydrolyzed protein crosses the placental barrier, causing bromoderma in the foetus [2] and transitory lethargy in the neonate [1]. A case was reported of a woman who had taken a mixture of bromides from the 39th week of pregnancy and in the 24 hours before birth. The mother had toxic delirium, and the infant was lethargic [1].

Bromides pass into breast milk [3], producing skin rashes and drowsiness in the infant [4]. After administration of 1 g bromide five times per day for 3 days to a nursing mother, 8 mg were found in 120 ml of milk [3]. Bromides should therefore be used with care during lactation.

No experimental studies have been described on the use of bromides in pregnancy in laboratory animals.

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Angiotensinamide

asp- β -amide of val-5-hypertensin II (MW 1030.71)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Angiotensin II, a pharmacologically active octapeptide, is derived from angiotensin I, an inactive decapeptide. This, in turn, is formed from angiotensinogen by means of renin, and is a plasma α -2-globulin. Angiotensin is considered the most potent pressor agent known, and is used in the therapy of shock. It has many pharmacological actions. These include vasoconstriction of precapillary arterioles, particularly in the skin, splanchnic, and renal areas, and a positive inotropic action on the heart, an increase in central arterial and venous pressure, an increase in vascular permeability with blood concentration, stimulation of ADH production, stimulation of sympathetic ganglion cells with increase in noradrenaline, and stimulation of the biosynthesis and storage of aldosterone in the adrenal cortex. The mechanism of action of angiotensin at the cellular level is similar to that of other biogenic amines, but on specialized receptors. Studies on the homeostatic role of the renin—angiotensin—aldosterone

system in regulating arterial pressure, natraemia, and vasal tone have progressed well beyond its therapeutic use.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1]. However, we advise care in the use of angiotensinamide in pregnancy because of its mechanism of action.

In the hamster, angiotensin was teratogenic. This was attributed to reduction of uterine blood flow or to release of catecholamines which can cause mitosis in embryonic tissue [2,3]. An intravenous infusion of 0.02–1.7 mg/kg (the therapeutic dose is 0.01–0.2 µg/kg/minute) administered on the 8th day of gestation caused malformations of the cranium, the brain, and the viscera [2,3].

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* * * * *

Antihaemorrhagic factor

non-saponifiable fraction of mammalian liver

Laevocystine

(MW 212.18)

This substance has been used in the therapy of hypoproteinaemia, intoxication, poisoning, and dermatoses.

Ethanolamine phosphate

phosphorylcholine (MW 159.12)

Phosphorylcholine is a precursor of acetylcholine and can activate the biosynthesis of the latter.

We have been unable to find any information on the use of these drugs in pregnancy, either in the literature or from the manufacturer. Although there have been no reports of adverse effects, we believe that they should not be used in pregnancy, or in women of childbearing age who are likely to conceive.

2. VITAMINS, COENZYMES, NUCLEOTIDES

The following drugs are discussed in this chapter:

	Recommendation	Page
Thiamine	NC	246
Prosulthiamine	NC	246
Thiamine disulphide	NC	246
Monophosphothiamine	NC	246
Cocarcboxylase	NC	247
Thioctic acid	NC	248
Riboflavine	NC	248
Pyridoxine	NC (C during lactation)	249
Cyanocobalamin	NC	250
Hydroxycobalamin	NC	252
Cobamaide	NC	252
Nicotinamide	NC	253
Nicotinic acid	NC	253
DPN or NAD	NC	254
Panthenol	NC	255
Coenzyme A	NC	256
Folic and folinic acid	NC	256
Biotin	NC	257
Troxerutin	NC	258
Flavodic acid	NC	258
Adenine	NC	259
Adenosine triphosphate	NC	259
Inosine	NC	260
Cogalactoisomerase	NC	261
Ascorbic acid	NC	261
Retinol	NC	262
Cholecalciferol	NC	265
Ergocalciferol	NC	265
Tocopherol	NC	267
Phylloquinone	P	269
Menaquinone	P	269
Menadione	P	269
Clupadonic acid	NC	271
Polyenic acid	NC	271

It should be emphasized that no vitamin, coenzyme, or nucleotide is contra-indicated in pregnancy. On the contrary, administration of these is essential in order to avoid damage to the mother, the pregnancy, and the foetus, since deficiency states are very common and difficult to diagnose.

Only in the case of the lipid-soluble vitamins A, D, and K is it necessary to control their administration in pregnancy, since hypervitaminosis could occur, and would be dangerous to the infant.

We do not think that there is sufficient evidence of safety to recommend the use of the following drugs in pregnancy: para-aminobenzoic acid, dihydrotachysterol, uridinetriphosphate (see pages 272–273).

Thiamine or vitamin B₁

(MW 300.81)

Prosulthiamine

dithiopropylthiamine (MW 356.51)

Thiamine disulphide

thiamine disulphide monohydrochloride (MW 562.72)

Not contra-indicated in pregnancy.

Thiamine or vitamin B₁ is the precursor of the coenzyme cocarboxylase and has no pharmacological actions. Its physiological role is that of facilitating the decarboxylation of the alpha-ketoacids and the utilization of the pentoses. Thiamine requirement is linked to glycide catabolism. Cases of hypersensitivity to parenterally administered thiamine have been described. This vitamin is activated by ATP and transformed into diphosphothiamine or cocarboxylase (see page 247).

During pregnancy, the thiamine daily requirement increases by 1–1.3 mg and thus it is possible for symptoms of deficiency to appear (polyneuritis). Thiamine crosses the placental barrier and tends to accumulate in the foetus. Foetal blood, in fact, has a higher concentration than maternal blood [1, 2, 3, 4, 5]. No foetal damage has been reported following hypervitaminosis B₁ in pregnancy [6]. On the contrary, hypovitaminosis B₁ is more common. Treatment with thiamine disulphide is thus advisable in pregnancy because it is more rapidly absorbed than vitamin B₁ itself [7, 8, 9]. Our own clinical experience supports the view that thiamine is innocuous in pregnancy. Therapy with vitamin B₁ is advised in hyperemesis gravidarum in order to avoid neurological complications [10, 11].

Vitamin B₁ passes into breast milk in a dose-dependent manner, particularly following administration of thiamine disulphide [12, 18].

In the mouse, rat, rabbit, and guinea-pig, high doses of thiamine reduced fertility and disturbed lactation, with loss of maternal instinct not only in the treated animals but in successive generations [13]. In the mouse, thiamine was

also teratogenic [15]. Intravenous doses of 0.5 mg given in a single administration on the 8th day of gestation caused malformations of the brain and the spine [15]. Transplacental passage of vitamin B₁ has been demonstrated in the guinea-pig [17].

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Monophosphothiamine

monophosphoric ester of thiamine (MW 380.82)

Not contra-indicated in pregnancy.

Monophosphothiamine has a neurotrophic action in that it improves cellular metabolism especially in the central nervous system.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been reported on the use of monophosphothiamine in pregnancy in laboratory animals.

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Coccarboxylase or diphosphothiamine

pyrophosphoric ester of vitamin B₁ (MW 422.21)

Not contra-indicated in pregnancy.

The pyrophosphate of thiamine or diphosphothiamine is the coenzyme which decarboxylates pyruvic acid and α -ketoglutaric acid, and utilizes the pentose involved in the hexose monophosphate shunt. Thus cocarboxylase is necessary in proportion to the increase in glycidic metabolism.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3], and our own experience supports this. Cocarboxylase has been used in labour together with sodium and potassium citrate, with improvement in metabolic acidosis in the mother, and no harmful effects on the foetus. Cocarboxylase did not affect the progress of the birth [4].

No experimental studies have been described on the use of cocarboxylase in pregnancy in laboratory animals.

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Thioctic acid or lipoic acid

5-(1,2-dithiolan-3-yl)-valerianic acid (MW 206.3)

Not contra-indicated in pregnancy.

Alpha-lipoic acid is connected with thiamine by the oxidative decarboxylation of the corresponding alpha-keto acid and in particular of pyruvate to acetyl coenzyme A. Lipoic acid is usually bound covalently (amide) to the lipoyl-reductase-transacetylase (liopamide) enzyme system and is therefore an essential constituent of the organism. Deficiency of this system is unknown. Lipoic acid has been used in the treatment of hepatic disease.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been described on the use of lipoic acid in pregnancy in laboratory animals.

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Riboflavine or vitamin B₂ or vitamin G

6,7-dimethyl-9-(D-1'-ribityl)-isoalloxazine (MW 367.36)

Not contra-indicated in pregnancy.

Riboflavine is transformed by ATP into two coenzymes, flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD), which are necessary for cellular respiration. In the respiratory chain, there are two flavoproteins which contain FAD, and which are transporters of hydrogen. FAD is necessary

also because of its role in beta-oxidation of fatty acids, and for its transformation of proline into glutamate. FMN intervenes in the deamination of the amino acids, which leads to the formation of alpha-keto-acids, since it is a coenzyme of 1-amino acid oxidase. Riboflavin does not possess a true pharmacological action apart from its biological role. For this reason, its therapeutic use is limited to treating symptoms of deficiency. The daily requirement is 1.5 mg, and this increases in pregnancy and during lactation.

No reports have been found of hypervitaminosis B₂ in pregnancy [1,2]. Riboflavin administered to lactating women passes into the milk [5], but only some time after the birth. When oral therapy is used, the concentration in the milk varies little, but it increases after intravenous administration [3].

In the rat, administration of riboflavin in pregnancy had no embryofoetotoxic or teratogenic effects [4]. Intraperitoneal administration of riboflavin at a dose of 20 mg/kg on the 12th day of pregnancy was innocuous [4].

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Pyridoxine or vitamin B₆

Complement Continus, Benadon, Optimax, Ancoloxin
5-hydroxy-6-methyl-3,4-pyridinmethanol (MW 169.17)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic					C

Not contra-indicated in pregnancy, but is contra-indicated during lactation.

Pyridoxine is present in nature in three forms, pyridoxin, pyridoxal, and pyridoxamine, all of which are utilizable in the synthesis of the coenzyme pyridoxal phosphate, with consumption of ATP. Isoniazid inhibits this activation and also the action of pyridoxal phosphate, and may therefore be considered as an antagonist of pyridoxine.

Pyridoxine has no specific pharmacological actions, but its biological role is fundamentally important for metabolism of the amino acids, in particular for their decarboxylation, transamination, and racemization, for metabolism of tryptophan, of the sulphurated amino acids, and of the hydroxyamino acids.

Pyridoxylphosphate is necessary for the synthesis of cysteine and thus for the synthesis of proteins and of glutathione, for the transformation of tryptophan into niacin, which is particularly active during pregnancy, and for the formation of phosphorylase. It is also required for the synthesis of glycogen, for the synthesis of the sphingolipids, for processes of transmethylation, and for the synthesis of GABA which is an inhibitory transmitter in the central nervous system.

Vitamin B₆ requirement is proportional to consumption of proteins, and is about 2 mg/day. It increases during pregnancy and lactation to 2.5 mg/day, and during therapy with isoniazid, hydralazine, oestrogens, and oral contraceptives. Administration of vitamin B₆ is contra-indicated during therapy with L-dopa, because it increases amino acid-decarboxylase which accelerates the transformation of L-dopa to dopamine.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, despite the wide use of vitamin B₆, at high doses and for long periods during pregnancy [1, 2, 6], and our own clinical experience is similar.

Pyridoxine depresses milk secretion; in fact, pyridoxal phosphate is the co-enzyme of DOPA-decarboxylase which catalyses the transformation of L-dopa to dopamine. The latter inhibits the production of prolactin by stimulating formation of prolactin inhibiting factor (PIF) [3, 4]. Pyridoxine is a component of milk, in which it often reaches a concentration of 15–20 µg/100 ml. After a single dose, the concentration of pyridoxine is tripled. It returns to normal levels within 9 hours, while continuous administration causes an accumulation which diminishes over 3 days [5].

In laboratory animals, massive doses of pyridoxine proportional to the degree of deficiency produced epileptic syndromes with interruption of pregnancy [1, 2].

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Cyanocobalamin or vitamin B₁₂

Cytacon, Cytamen, Hepacon B₁₂ (MW 1355.42)

Not contra-indicated in pregnancy.

Cyanocobalamin is the stable form of an extract of vitamin B₁₂. In the organism, the coenzyme form cobamamide, which is metabolically active, is present. However, hydroxycobalamin is also produced commercially, with

an OH group in place of CN. These forms have diverse actions compared to cyanocobalamin and are less stable.

Vitamin B₁₂ is not only one of the essential factors in haemopoiesis, but has many biological applications. It participates in the synthesis of the nucleic acids, when its requirement is proportional to the degree of cellular proliferation, particularly in those tissues which grow rapidly (e.g., epithelium). It enters into the biosynthesis of myelin, which is a lipoprotein, influencing the formation of both the lipid and the protein components. Vitamin B₁₂ is also essential for inter-conversion of methylmalonate to succinate and of homocysteine to methionine. The latter process also involves folic acid; lack of vitamin B₁₂ causes an accumulation of methylfolate, thus leading to a functional shortage of this vitamin and a block of monocarbon unit metabolism.

Vitamin B₁₂ stimulates protein synthesis by regulating the synthesis of methionine and probably of other amino acids. Its lipotropic action is mediated via a similar mechanism. Vitamin B₁₂ contributes to maintaining sulphhydryl groups in a reduced state, thus activating all enzymes which involve these groups.

During pregnancy and lactation, the daily requirement of vitamin B₁₂ increases by about 2–3 µg. Vitamin B₁₂ crosses the placental barrier [1] and reaches blood levels in the foetus at birth which are sometimes higher than those in the mother [1, 2, 3]. In toxæmia, the maternal and foetal concentrations of vitamin B₁₂ are low [3]. Vitamin B₁₂ passes into breast milk [4, 5, 6, 7, 12], reaching concentrations of 0.1–0.3 µg/l. Administration of cyanocobalamin during pregnancy, even at high doses, is neither embryofoetotoxic nor teratogenic [8]. It induces an increase in antibodies and total proteins in the foetus, as well as albumin and gamma-globulins [9]. Our own clinical experience is similar.

In the rat, oral administration of vitamin B₁₂ at doses of up to 1000 µg/kg in the diet, or subcutaneous doses of 100 µg once per week, were not toxic and did not affect reproduction [10].

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Hydroxycobalamin

(MW 1347.36)

Not contra-indicated in pregnancy.

Hydroxycobalamin has an identical pharmacological action to cyanocobalamin (see page 250) in being able to produce haematological response, but as it is strongly bound to plasma proteins, it has a more prolonged duration of action.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3], and our own clinical experience confirms this. Treatment of 19 pregnant women with neuritis with doses of 1 mg hydroxycobalamin intravenously for 4, 5, or 6 days at various stages of pregnancy caused no side effects in the mother or the foetus [4].

No experimental studies have been described on the use of hydroxycobalamin in pregnancy in laboratory animals.

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Cobamamide

5, 6-dimethyl benzimethazol cobamide coenzyme (MW 1579.57)

Not contra-indicated in pregnancy.

Cobamide is the native form of vitamin B₁₂ coenzyme or cyanocobalamin, of which it is the forerunner (see cyanocobalamin, page 250).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3, 4, 5].

In the rat and rabbit, cobamamide had no embryofoetotoxic or teratogenic effects [1, 2]. In the rat, subcutaneous doses of 0.1–10 mg/kg did not affect fertility or the development of the pregnancy. There were no foetal resorptions, and the foetuses were normal [1, 2]. In the rabbit, oral doses of 1 mg/kg had the same results [1, 2].

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Nicotinamide or niacinamide or vitamin PP

pyridine-3-carboxamide (MW 122.1)

Nicotinic acid or niacin

Pernivit, Equivert, 3-pyridinecarboxylic acid (MW 123.1)

Not contra-indicated in pregnancy.

Nicotinic acid is the precursor of 2 pyridine coenzymes, which include NAD and NADH. These may also be derived from nicotinamide and, to a lesser extent, from tryptophan. In addition to its physiological role, nicotinic acid, like nicotinic alcohol, also has specific pharmacological activity. It is a cutaneous vasodilator, particularly in the upper half of the body, a hypotensive, and a regulator of plasma lipids. In adipose tissues, it reduces accumulation of cyclic AMP which activates triglyceride lipase. This results in a diminished release of free fatty acids, a reduced hepatic triglyceride biosynthesis, and thus lower levels of plasma triglycerides. On the other hand, nicotinic acid accelerates removal of triglycerides present in plasma by activation of lipoprotein lipase, in a similar manner to heparin.

Nicotinamide is deaminated to nicotinic acid in the liver. Excessive doses of nicotinic acid may diminish the available amount of methyl groups in the organism (*N*-methylnicotinamide is the principal metabolite) and thus lead to hepatic changes with jaundice and increase in plasma transaminases. Nicotinic acid can induce the appearance of hyperglycaemia, reduced tolerance to glucose, and hyperuricaemia. It is used to treat hypercholesterolaemia, coronary disease, and arteriosclerosis.

Pregnancy causes niacin deficiency as can be demonstrated by oral loading [1]. In fact, niacin requirement is slightly increased. In pregnancy, niacin has been used as a vasodilator, in the treatment of toxæmia and eclampsia [2, 3] to resolve generalized vasospasm, and to lower plasma cholesterol levels [4]. In the course of such treatment, no maternal or foetal side effects were encountered, nor was there any case of malformation [5, 6, 7, 8]. Our own clinical experience has been similar. It has been reported that intravenous injection of sodium nicotinate during Caesarian section did not affect uterine kinetics [2]. Niacin has also been used in the therapy of hypogalactia, because it can resolve this condition without affecting the composition of the milk [9, 10, 11, 12, 13], even although it is excreted in milk [20].

Niacin has been studied in the rat, rabbit, and chick embryo. It was not teratogenic in the rabbit, at a dose of 300 mg throughout pregnancy [5, 14]. In chick embryo, nicotinic acid injected at doses of 20 mg in the 2nd, 3rd, and 4th days of incubation was teratogenic, causing defects of closure of the neural tube, and cardiovascular malformations [17]. At doses of 1.5 grams given after 96 hours of incubation, nicotinic acid was not teratogenic [19]. Other experimental work has established that in the rat, the placenta contains a low amount of

pyridine coenzymes [15], and that in the pregnant rabbit, on the contrary, the highest levels of nicotinic acid were found in the utero-placental unit [16].

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DPN or NAD or nadide

diphosphopyridine nucleotide or niacinadenine dinucleotide (MW 663.44)

Not contra-indicated in pregnancy.

NAD is one of the principal coenzymes of cellular respiration, and is synthesized from niacin (see page 253). NAD in turn is transformed into its phosphoderivative, TPN or NADP. The biological importance of these coenzymes is evident from the following examples. NAD is essential for metabolism of ketone bodies, in particular the reduction in the mitochondria of acetoacetate to β -hydroxybutyrate, for the desaturation or retroconversion and the α - and β -oxidation of fatty acids, for the oxidation of proline, and for the synthesis of pyranose-monophosphate.

NADP in the reduced form (NADPH) is formed in the hexose monophosphate shunt and in reactions catalysed by malate and isocitric dehydrogenases. It is also involved in the reductive syntheses of cholesterol (reduction of HMGCoA or 3-hydroxy-3-methyl-glutaryl CoA and mevalonate), fatty acids, and sphingosine necessary for the formation of the sphingolipids of the nervous system. NADP is also necessary for hepatic catabolism of pyrimidine bases (citicholine, uracil, thymine), for the hydroxylation of the steroids, for Ω -oxidation of fatty acids, for metabolism of glucuronate to ascorbate, for

the gluco-fructose interconversion, for the first two steps in the pentose shunt, and for the transformation of maleate to oxalacetate.

Lipogenesis is regulated by the concentration of NADPH. The energy produced in the respiratory chain is stored in the form of ATP, and beyond a certain limit, slows down anaerobic glycolysis while activating the pentose shunt. In this way, a larger quantity of NADPH is synthesized, which activates the biosynthesis of fatty acids. DPN or NAD may be used to activate cellular respiration in ischaemic cardiac disease and in the hepatopathies, in addition to having similar therapeutic applications as niacin.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, the same considerations apply as for niacin (page 253).

No experimental studies have been described on the use of NAD in pregnancy in laboratory animals.

Panthenol or panthetin or despanthenol or pantothenic acid

d-pantothenylic acid (MW 205.25)

Not contra-indicated in pregnancy.

Pantothenic acid is an integral part of coenzyme A which favours the biosynthesis of acetylcholine by catalysing the acetylation of choline. Pantothenylic alcohol is more stable than pantothenic acid. This substance is essential for normal functioning of the parasympathetic nervous system. Compared to neostigmine, it does not produce an excess of acetylcholine. Acetylcholine is necessary for normal intestinal and visceral motility, and therefore pantothenyl alcohol is used in the treatment of intestinal atonia.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3,4,5], and our own clinical experience is similar. A study on 444 patients with cramps in the lower limbs at various stages of pregnancy, who were treated with pantothenic acid for 10 consecutive days at a dose of 400 mg/day, showed remission of symptoms in 57% of cases and an improvement in 20%, with no side effects in the mother or the foetus [4]. Similar results were obtained in another group of 30 patients [5].

No experimental studies have been described on the use of pantothenic acid in pregnancy in laboratory animals.

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Coenzyme A or pantadephosphate

(MW 767.55)

Not contra-indicated in pregnancy.

Coenzyme A represents the active form of pantothenic acid and functions by facilitating transfer of two carbon (acetyl) units which are transported by means of its sulphhydryl group. In the mitochondria, coenzyme A catalyses the formation of oxalacetate and then initiates the tricarboxylate acid cycle, a common oxidative route for the metabolism of glucide, lipid, and proteins.

Blood pyruvate levels increase [1] during pregnancy, particularly in toxæmia, eclampsia, and hyperemesis. Administration of coenzyme A in these cases reduces blood pyruvate and lactate [2], because these metabolites arise as a result of oxidative decarboxylation, thus improving symptomatology. No reports of foetal side effects have been found, and this is not surprising, since coenzyme A is normally present in mitochondria, and pantothenic acid, from which it is derived, is essentially innocuous [3].

No experimental studies have been described on the use of coenzyme A in pregnancy in laboratory animals.

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Folic and folinic or pteroylglutamic acids

Co-Ferol, Fefol, Folex-350, etc. (MW 426.36)

Not contra-indicated in pregnancy.

Folic or pteroylglutamic acid is composed of a pterin, one molecule of para-amino-benzoic acid, and one or more molecules of glutamic acid. It represents the inactive form, present in nature, of a coenzyme, tetrahydrofolic acid, which catalyses transport of monocarbon units (formyl, formimino, methylene, methenyl, methyl). 5-formyl-tetrahydrofolic acid, also called folinic acid or citrovorum factor, represents one form of the coenzyme.

The biological action of folic acid, which in some respects is linked to that of vitamins B₆ and B₁₂, is complex and may be summarized as follows: (a) synthesis of purine, (b) synthesis of the pyrimidine nucleotides, (c) regulation of the formate pool, (d) interconversion of some amino acids (serine—glycine, histidine—glutamic acid, homocysteine—methionine). For the first of these, pyridoxine is required, and for the last, cyanocobalamin.

Folic acid consumption is closely linked to the rate of mitosis and of protein metabolism, and is thus greater in rapidly growing tissues such as foetal bone marrow, placenta, and neoplasms. In fact, one of the signs of deficiency is a characteristic megaloblastic anaemia in pregnancy. Pregnancy and lactation

double folic acid requirement, which is normally around 200 $\mu\text{g}/\text{day}$, and which further increases if there is a multiple pregnancy. Many drugs increase folic acid requirement, including anticonvulsants, pyrimethamine, trimethoprim, triamterene. There are also antimetabolites of folate, such as amethopterin, which act competitively.

Folic acid deficiency during pregnancy, induced either by lack of folate in the diet or as a result of concurrent drug administration, may lead to the appearance of foetal malformations and a state of imbalance in trophoblastic cells, which have a particularly high requirement for folate, to the extent of causing sudden detachment of the placenta. Administration of folic acid is not harmful to the foetus, the mother, or the pregnancy [1, 2, 3], and our own experience confirms this.

Folic acid passes into breast milk [4].

In laboratory animals, transplacental passage of folic acid has been demonstrated, but no side effects have been reported following its use in pregnancy.

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Biotin or vitamin H₁ or pabacid

D- β -biotin (MW 244.31)

Not contra-indicated in pregnancy.

Biotin is normally available in sufficient quantity to meet requirements. Deficiency in man may be observed only after administration of large doses of albumin, or by the action of drugs which destroy intestinal flora. The physiological role of biotin is complex. It is involved in processes of carboxylation (for fixation of CO_2), of decarboxylation, and of oxidative de-amination of some amino acids. Biotin is nontoxic, and its therapeutic use, which has not always been approved, has been limited to skin diseases involving disorders of keratinization and sebum production.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of biotin in pregnancy in laboratory animals.

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Troxerutine or vitamin P or oxerutine

Paroven, *O*-(β -hydroxyethyl)-rutoside A (MW 742.7)

Not contra-indicated in pregnancy.

Troxerutine is a flavonoid derivative which inhibits adrenaline catabolism, diminishes vascular permeability, and increases the tone of the vascular walls by a sympathomimetic action [1].

Troxerutine has no foetotoxic or teratogenic effects [2] in man, and it does not affect the contractions of the uterus [2, 3]. It is harmless in pregnancy [2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15].

No experimental studies have been described on the use of troxerutine in pregnancy in laboratory animals.

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Flavodic acid

sodium benzo- γ -pyrone 2-phenyl-5,7-dioxyacetate (MW 314.31)

Not contra-indicated in pregnancy.

Flavodic acid is a biflavonide with a capillary protective action. It has been proposed that these drugs, which are considered by some to be vitamins, slow down catabolism of catecholamines which decrease permeability [4].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3].

No experimental studies have been described on the use of flavodic acid in pregnancy in laboratory animals.

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Adenine

(MW 135.14)

Not contra-indicated in pregnancy.

Adenine is a purine base which enters into the composition of numerous molecules of fundamental biological importance. It is synthesized in the organism and thus is not really a vitamin of the B complex. It has, however, been demonstrated that adenine is used in the biosynthesis of nucleic acids by normal and immature leucocytes [1], and its deficiency may give rise to agranulocytosis. Adenine, unlike ATP and ADP, enters the cells and may be utilized for the biosynthesis of these compounds [2]. It has been shown that adenine has a protective action against the effects of radiation. Adenine is used to treat agranulocytosis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [4, 5, 6], and the manufacturers have confirmed this [3].

No experimental studies have been described on the use of adenine in pregnancy in laboratory animals.

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Adenosine triphosphate or ATP

(MW 507.21)

Not contra-indicated in pregnancy.

ATP is a donor of energy, which is necessary, among other things, for muscle contractions. In the uterus, ATP has an oxytocic action, Administered intravenously, it has a vasodilator action, as have other adenine compounds.

ATP is used in the therapy of cardiopathies in pregnancy [5], in the prophylaxis of toxæmia [6], and in foetal distress. In fact, it increases uterine blood flow [8], improving the oxygenation of the foetus as a consequence [9]. ATP has also been used in labour to intensify uterine contractions. Intravenous or intramuscular administration is synergistic with oxytocic hormones [1]. Previous *in vitro* experiments have demonstrated that the action of ATP on

fragments of human myometrium taken during the course of Caesarian section was to cause contraction [2]. Administration of ATP during labour is completely harmless to the foetus and the mother [2, 3, 4], and our own clinical experience is similar.

ATP alone was less active than oxytocin in inducing labour [3]. It was shown to be effective in foetal distress during labour. Administration of 20–40 mg intramuscularly improved foetal metabolism in hypoxia by increasing oxygen concentration, diminishing carbonic anhydride and lactate, and normalizing foetal pH. The Apgar score at birth is usually normal following such treatment. An intramuscular dose of 40 mg had no effect on uterine contractions. The vasodilator and antispastic actions of ATP have been used in the therapy and prophylaxis of puerperal vascular disorders [7].

In laboratory animals, ATP was useful in foetal hypoxia [10, 11]. ATP administered from the 11th to the 14th day of pregnancy reduced the incidence of foetal malformations (hydrocephalus, defects of the vertebral column, eye defects) produced by the simultaneous administration of cortisone acetate at a dose of 2.5 mg [12].

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Inosine

(MW 268.23)

Not contra-indicated in pregnancy.

Inosine is a nucleotide which is used by the cells for the synthesis of ATP and therefore has the same biological importance as ATP. Inosin also inhibits the biosynthesis of porphyrin and stimulates erythropoiesis. It has a slight hypotensive action, and is used as a myocardiotropic drug [1].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the chick embryo, inosine was teratogenic [2] at very high doses. At 4 days' incubation, doses of 2–8 mg ($LD_{50} = 4-8$ mg) caused various malformations with an incidence of 9% [2].

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Cogalactoisomerase

uridine-5-diphosphoglucose (MW 566.3)

Not contra-indicated in pregnancy.

Uridine-5-diphosphoglucose (UDPG) as a precursor of uridine-5-diphosphoglycuronic acid (UDPGA) is vital for glucuronide conjugation of numerous endogenous and exogenous substances in the organism. Its mechanism of action is such as to produce more rapid elimination of a quantity of indirect bilirubin [2] in the adult, and to cause a more rapid fall in physiological hyperbilirubinaemia in the neonate [3].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, administration of cogalactoisomerase shortly before parturition resulted in an increased hepatic capacity for conjugating bilirubin in the neonate [1].

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Ascorbic acid or vitamin C

Redoxon, etc. (MW 176.12)

Not contra-indicated in pregnancy.

Ascorbic acid is a natural anti-oxidant which can be synthesized from glucose in some species of animals but not in man. Its biological action is to create a reducing environment useful for maintaining the sulphhydryl enzyme in an active state. This enables folic acid to be transformed into tetrahydrofolic acid, and facilitates intestinal absorption of iron, protects adrenaline from oxidation in the adrenal medulla, and facilitates hydroxylation of proline and of lysine, necessary for the biosynthesis of collagen. Ascorbic acid is also involved in the metabolism of excess tyrosine, for respiratory activity in the adrenal cortex together with the biosynthesis of steroids, and for the metabolism of glucides. Because of its anti-oxidant properties, ascorbic acid is used to preserve foodstuffs.

In pregnancy and lactation the requirement for ascorbic acid increases from 45 to 60 mg and 80 mg/day respectively. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy related to administration of ascorbic acid [1, 2, 12, 13, 14]. However, when high doses are administered

to the mother, it is theoretically possible that scurvy could occur in the infant [3].

Ascorbic acid passes into breast milk [4, 15].

In the guinea-pig, mouse, and rat, ascorbic acid could be teratogenic and harmful to the pregnancy [5, 6, 7, 9]. In the guinea-pig, hypervitaminosis C caused disturbances of pregnancy leading to foetal death and subsequent infertility [5, 6]. However, there did not appear to be a true embryofetotoxicity [6]. In the mouse, intravenous doses of 20 mg on the 8th day of pregnancy caused a significant increase in malformations of the brain and spinal column [7]. In the rat, doses of 1 g/kg from the 6th to the 15th day or throughout pregnancy were not harmful to the foetus [9].

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Retinol or axerofthol or vitamin A

Ro-A-Vit (MW 286.44)

Not contra-indicated in pregnancy.

Vitamin A can occur in two forms, both as provitamins (carotenes), and in various stages of oxidation (alcohol, aldehyde, acid), and in the various stereoisomers, *cis* and *trans*. The biological role of vitamin A is linked principally to the process of vision. *Cis*-retinol is oxidized to *cis*-retinal, and this links to a protein (opsin in the rods and photopsin in the cones) to form respectively rodopsin and iodopsin. As a result of the effect of light, *cis*-retinal is transformed into *trans*-retinal, which separates from the protein, releasing sufficient chemical energy to provide nervous stimulation. The process is reversible in all senses (*cis-trans* and alcohol-aldehyde).

The three forms (retinol, retinal, retinoic acid) also have importance in almost all cells. They regulate the biosynthesis of glycoproteins (mucopolysaccharides), principally at the level of collagen and of the muciparous structures;

regulation of keratinization of the epithelium, of permeability of the cellular membrane, of lysosome function, of cholesterol synthesis, and of interconversion of the steroid hormones. In addition, they play a role in the biosynthesis of nuclear RNA and thus in the transcription of the genetic code and in cellular differentiation.

The serious consequences which follow a lack or overdosage of vitamin A are therefore understandable. In the latter case, probably as a result of therapeutic error, increased permeability of cell membranes leads to swelling of the mitochondria and the lysosomes. Proteases are released, and these split the mucopolysaccharides. By modifying the synthesis of nuclear RNA, the development of the bone matrix and interconversion of steroids, hypervitaminosis A affects fertility and the development of the embryo.

The requirement for vitamin A is increased during pregnancy, but its plasma levels are reduced because consumption is greater than the amount mobilized from hepatic reserves. Retinol crosses the placental barrier [1, 2, 32] and reaches a lower concentration in foetal plasma than in the mother. The placenta, within certain limits, hinders the excessive passage of vitamin A and of its provitamins. Vitamin A is secreted in breast milk in a concentration which is relatively constant, even if this depletes hepatic reserves [11].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy as a result of administration of vitamin A in therapeutic doses. Our own clinical experience is similar. Other authors are agreed that overdosage with vitamin A can cause embryofetotoxic and teratogenic effects, including abortion, cataract, malformations of the urogenital tract, malformations of the middle and external ear, cleft palate anencephaly, cortico-hyperostosis, etc. [2, 3, 4, 5, 7, 8, 9, 10, 34, 37]. Administration of 40 000 IU vitamin A per day for 1 month at the beginning of pregnancy caused the birth of a foetus with serious malformations of the urogenital tract attributable to overdosage [9]. A case is described of renal malformations in the infant of a patient who had taken 25 000 IU vitamin A in the first trimester of pregnancy and 50 000 IU in the 4th and 9th months [10]. The case is reported of a twin with cortical hyperostosis, radiologically diagnosed during the pregnancy, who was born to a mother who had taken 10 000 IU vitamin A throughout pregnancy [31].

Passage of Vitamin A into breast milk has been demonstrated [11, 35].

In the rat, mouse, rabbit, hamster, and guinea-pig, overdosage with vitamin A caused noticeable embryofetotoxic and teratogenic effects [4, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 36]. In the rat, administration of 35 000 IU vitamin A from the 2nd to the 16th day of pregnancy resulted in an incidence of 52% anencephaly and polyhydramnios, and 38% cleft palate and ocular malformations [16]. Administration of vitamin A at doses of 60 000 IU at various stages of pregnancy caused anencephaly, spina bifida, anophthalmia, and microphthalmia [19]. Doses of 50 000 IU from the

8th to the 10th day of pregnancy produced anencephaly, microphthalmia, cleft palate and hydronephrosis [22]. Administered at high doses from the 8th day of pregnancy, vitamin A caused defects in closure of the neural canal, while administration from the 11th day caused an increased incidence of cleft palate and skeletal defects [23].

In the mouse, administration of vitamin A at a dose of 60 000 IU for 3 days during pregnancy caused cleft palate in the fetuses [12]. Administered at a dose of 50 000 IU from the 10th to the 13th or the 8th to the 10th or the 11th to the 13th day of pregnancy, vitamin A caused anencephaly and cleft palate [26].

In the rabbit, doses of 41 000, 80 000, or 160 000 IU from the 5th to the 14th day of pregnancy caused 100% abortions at the highest dose, and 50% at the middle dose, with some malformations (renal agenesis, microstomia, etc.). At the lowest dose, there were only malformations, including atrophy of the lower jaw, exophthalmia and crystalline haemorrhage, cleft palate, and ectrodactyly. It was concluded that hypervitaminosis A in the rabbit was more likely to cause abortion than malformations [33]. Administration of vitamin A at doses between 150 000 and 500 000 IU from the 5th to the 10th day of gestation caused exencephaly, anencephaly, microphthalmia, anophthalmia, and syndactyly [26].

In the guinea-pig, doses of 50 000 IU from the 10th to the 13th day of pregnancy caused the appearance of exencephaly in the fetuses [26].

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Cholecalciferol or vitamin D₃

(MW 384.62)

Ergocalciferol or vitamin D₂

Chocovite (MW 396.63)

Not contra-indicated in pregnancy.

Cholecalciferol or vitamin D₃ is synthesized in the organism, starting from 7-dehydroxholesterol, by the photochemical action of sunlight. Deficiency of this vitamin occurs only when there is a lack of exposure to the sun. In these conditions, the action of vitamin D₃ may be effected by the introduction into the diet of an adequate quantity of vitamin D₂ or calciferol. In fact, there is no difference between the effects of vitamins D₃ and D₂.

Calciferol or ergocalciferol or vitamin D₂ is derived from ergosterol, a provitamin, by ultraviolet radiation.

The D vitamins do not react as such, but are further metabolized in the liver and kidneys to more active substances. This involves firstly hydroxylation in the liver in position 25 of the molecule, leading to the final active compound, 25-OH-D₃, which is regulated by plasma concentrations. Within certain limits, this results in a protection from overdosage with vitamin D₃, and it avoids waste. A further hydroxylation occurs in position 1 in the liver, and this is regulated by plasma calcium ions. This produces 1,25(OH)₂ vitamin D₃, which represents the true active form.

The biological actions of the vitamin D group are interlinked with those of calcitonin and of parathormone in regulating the distribution of calcium in various compartments within the organism. Part of the calcium is involved in mineralization of bone, while the rest is principally involved in metabolism. Calcium is essential for regulating neuromuscular excitability, coagulation, the rate of certain enzymic reactions, and to ensure the integrity of cellular

membranes. Vitamin A contributes to the homeostasis of calcaemia and influences the intestinal absorption of calcium and phosphorus.

There is a strict correlation between maternal and foetal levels of 25-OH-D₃ [10]. Vitamin D is not harmful to the foetus when administered during pregnancy in therapeutic doses [1, 26], and our own clinical experience is similar. Fifteen patients with hypoparathyroidism were treated with an average dose of 107 000 (\pm 10 500) IU vitamin D per day. Normal levels of calcium were maintained throughout pregnancy, and the infants were all healthy. Following a period of 4 years, it was demonstrated that no child had been born with cardiovascular or facial anomalies associated with infantile hypercalcaemia [1]. At therapeutic doses, vitamin D appeared to be safe in pregnancy [1].

The theory has been advanced, however, that vitamin D administered to pregnant women could cause congenital cardiovascular malformations [2], particularly supraventricular aortic stenosis, mental retardation, idiopathic hypercalcaemia, and diffuse osteosclerosis [3, 27]. Vitamin D in very high doses can give rise to extensive calcification of the placenta and in some cases can reduce the area of maternal-foetal interchange to the point of causing foetal distress [5, 6, 7, 8, 9]. An increase in duration of pregnancy, with heavier than normal foetuses [5], and hyperossification of the cranial bones (cause of distocia) and, more rarely, calcification in various organs, particularly the kidney [8], and stenosis of the pulmonary and renal arteries with arterial hypertension [9], have all been observed. A patient who had taken large quantities of vitamin D during pregnancy gave birth to a dead foetus with cerebral haemorrhage, probably because of compression as a result of the poor elasticity of the cranium [11].

The D vitamins pass into breast milk. High doses given to the mother cause an increase in concentration in the milk, up to levels sufficient to prevent rickets [12].

In the rat, guinea-pig, and rabbit, the D vitamins at high doses were teratogenic, and caused serious disturbances in calcium metabolism in the mother [14, 16, 17, 18, 20, 21, 22, 23, 24, 25]. In the rat, hypervitaminosis D during pregnancy caused micromelia and osteoporosis [14]. Excessive doses of vitamin D during pregnancy, associated with a diet lacking in minerals, stimulated bone decalcification [16]. Subtoxic doses of vitamin D, associated with a diet deficient in minerals during pregnancy, increased the calcium and phosphorus content of the neonates [17]. Vitamin D at doses above therapeutic given before the 5th day of pregnancy produced degeneration and resorption of the blastocysts, but if given after the 5th day, there was no damage to the foetus [18]. Maternal hypervitaminosis (40 000 IU) from the 9th day of gestation resulted in diminution in foetal weight and reduction in weight and volume of the ashes of foetal bones [20]. Further studies have demonstrated that half of the offspring of animals with hypervitaminosis D died during parturition or immediately after birth, while the survivors had imperfect osteogenesis with multiple fractures [21]. At a dose of 300 000 IU/kg during the last 9 days of pregnancy, vitamin D caused the

death of some fetuses, malformations of the jaws, retarded dentition, and foetal hypercalcaemia [22].

In the guinea-pig, doses of 12 000 IU/day produced a reduction in fertility, an increase in the number of fetuses, and an increase in postnatal deaths [23].

In the rabbit, doses of 1.5 million IU given intramuscularly on alternate days throughout pregnancy caused anomalies of the foetal aorta [24]. In earlier experiments, a foetal hydronephrosis was observed in the offspring of mothers treated with very high doses of vitamin D [25]. Transplacental passage of vitamin D has been shown. Hypervitaminosis D in pregnant animals increased blood levels of the vitamin, produced increased calcium, and caused the appearance of a supravalvular stenosis of the aorta in 14 cases out of 34 [4].

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Tocopherol or vitamin E

Ephynal, Vita-E,

d 1-2, 5, 7, 8-tetramethyl-2-(4', 8', 12'-trimethyltridecyl)-6-chromanol
(MW 430.69)

Not contra-indicated in pregnancy.

The action of vitamin E is similar to that of the tocopherols present in nature, which have structures analogous to that of coenzyme Q in the cellular respiratory chain. A large part of the activities of the tocopherols is related to their antioxidative properties, which prevent the oxidation of essential cellular constituents, in particular the formation of peroxides of the essential polyunsaturated fatty acids. An analogous action is also a property of the thiol amino acids and of coenzyme Q. The tocopherols also regulate the rate of synthesis of particular proteins which are necessary for cellular differentiation.

Vitamin E facilitates absorption, formation of reserves in the liver, and utilization of vitamin A. In some animal species, but not in man, vitamin E has been shown to be necessary for the development of pregnancy, for proliferation of the testicular germinative epithelium, for growth of striated muscle, and for haemopoiesis.

In obstetrics, vitamin E has been used in the treatment of habitual abortion, of male and female sterility, of toxæmia, of menstrual disturbances, and of the menopause. However, there is still no definite demonstration of its therapeutic value. The daily requirement is estimated at about 12 IU and does not substantially increase during pregnancy or lactation. Vitamin E is absorbed with the lipids, binds to beta-lipoproteins in the plasma, and is distributed in all tissues.

In neonates, plasma concentrations of vitamin E are 20% of those in the mother. Its passage across the placenta is probably very low [1].

There have been no reports of harmful effects on the human foetus, the mother, or the pregnancy, and our own clinical experience supports this view. One case has been cited of a patient who had swallowed 400 IU/day throughout pregnancy, with the intention of preventing anaemia in her infant. The baby was normal, and continued in good health when followed up for 1 year [2]. The hypothesis has been advanced that vitamin E, being an antioxidant, might prevent teratogenic effects [2].

Vitamin E administered to the mother at doses of 240 mg/day increased milk supply without its concentration significantly increasing in milk [3].

In the mouse, vitamin E could be teratogenic if administered subcutaneously [2, 4]. Subcutaneous doses of 150–300 mg/kg on the 6th, 8th, and 10th day of pregnancy caused cleft palate [4]. Doses of 19 700 IU/kg given orally from the 7th to the 11th day of pregnancy had an insignificant teratogenic effect (one out of 91 foetuses). Foetal growth rate was not affected [2].

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Phylloquinone or vitamin K₁ or phytomenadione

Konakion (MW 449.8)

Menaquinone or vitamin K₂

(MW 580.02)

Menadione or vitamin K₃

(MW 172.19)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P	P	

To be used with care in pregnancy.

The action of vitamin K is related to several compounds; phylloquinone or vitamin K₁, of vegetable origin, menaquinone or vitamin K₂, produced by intestinal flora, and menadione or vitamin K₃, of synthetic origin. There are various water-soluble derivatives of the latter substance, including menadione sodium bisulphate and menadione sodium diphosphate, which are converted to menadione in the organism.

Vitamin K stimulates the hepatic synthesis of factors II, VII, IX, and X of coagulation, and in particular initiates the incorporation of the glycidic prosthetic group into these glycoprotein molecules. Phylloquinone and menaquinone (K₁ and K₂) are absorbed in the digestive tract as lipids, that is, only in the presence of biliary cells, while menadione and its water-soluble derivatives do not present such problems. Deficiency of vitamin K occurs when there is inadequate intestinal absorption or a lack of hepatic utilization.

The K vitamins are toxic to the liver and kidneys, and can cause haemolysis if there is a coexisting congenital deficiency of erythrocyte glucose-6-phosphate dehydrogenase. In the immature neonate, vitamin K is only barely utilized, and this results in haemolysis, haemolytic anaemia, hyperbilirubinaemia, and jaundice. The K vitamins are antagonized by dicoumarols (oral anticoagulants).

The K vitamins cross the placental barrier [1, 2, 31] and produce an increase in prothrombin and proconvertin in the neonate [27]. Administration of very high doses of vitamin K in the water-soluble form to the pregnant woman in the last trimester and during labour can cause, both in premature births and in those at full term, serious haemolytic anaemia (with the appearance of circulating Heinz bodies), and serious hyperbilirubinaemia with nuclear jaundice [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 34]. This may be due to two causes: (a) vitamin K is eliminated in part as a glucuronide and competes with bilirubin for the mechanism of hepatic detoxification, which

is already limited in the neonate; (b) vitamin K may cause a haemolysis of the erythrocytes, particularly in neonates, with low concentrations of alpha-tocopherol. Seven out of nine infants of patients who had taken 72 mg menadione bisulphate sodium intramuscularly or intravenously shortly before the beginning of labour had hyperbilirubinaemia and needed transfusions [4]. A study on 38 neonates who had shown jaundice in the first hours of life (bilirubin of 5.2 mg at 16%) showed that all the mothers had taken vitamin K before the birth [3]. On the other hand, it has been shown that the natural K vitamins (liposoluble) are less toxic to the neonate than the synthetic menadione. An investigation of 933 pregnant women treated with 20 mg/day of natural vitamin K at the end of pregnancy showed that all gave birth to normal infants who had no symptoms of asphyxia or jaundice [29].

The water-soluble form of vitamin K passes into breast milk, but only in very small quantities [31].

In the rat and mouse, administration of synthetic vitamin K caused both embryofetotoxic and teratogenic effects [32,33]. In the rat, intramuscular doses of 10 mg vitamin K produced haemoglobinuria and hyperbilirubinaemia [33]. In the mouse, intramuscular doses of 0.5 mg/kg vitamin K from the 6th to the 11th day of pregnancy caused cleft palate and exencephaly [32].

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Clupadonic acid

7,10,13,16,19-decosapentenoic acid (MW 330.5)

Not contra-indicated in pregnancy.

Clupadonic acid is a polyunsaturated fatty acid which is extracted from cod liver oil, and which probably forms part of the lipids of nerve tissue. Therapeutically, it has been used as a 'reconstituent' in the same way as polyunsaturated fatty acids (the vitamin F complex), of which biosynthesis seldom supplies the requirement. Such acids form part of the phospholipid molecule of the cell wall, and are the starting point for the formation of the prostaglandins.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of clupadonic acid in pregnancy in laboratory animals, and the manufacturers have confirmed this.

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Polyenic acids or vitamin F

mixture of polyunsaturated fatty acids including
linolenic acid (MW 278.42) and arachidonic acid (MW 304.46)

Not contra-indicated in pregnancy.

The essential polyunsaturated fatty acids are linoleic and linolenic acids, which contain 18 carbon atoms with respectively two and 3 double bonds, and arachidonic acid, with 20 carbon atoms and 4 double bonds. Their biosynthesis differs between the animal and vegetable kingdoms. In plants, carbohydrates are the starting point, since it was noted that in the seeds there was an increase in lipids and a diminution in glucides. The reverse occurs during germination, when linoleic acid and linolenic acid are oxidized as a result of increased lipo-oxidase activity.

In animals, on the contrary, the synthesis of the essential fatty acids is a slow process and often inadequate (for this reason, they are termed 'essential'), and depends on the availability of pyridoxine (vitamin B₆). The liver and the testes are able to unsaturate fatty acids (retroconversion) because they contain a specific NAD-dependent enzyme. The tocopherols have the ability to protect essential fatty acids by virtue of their antioxidant action.

The polyenic acids are abundant in nature. They are found in all fats, especially those of vegetable origin (they occur in decreasing order in oil of wheatgerm, cotton seed, peanut, olive, in fat, in butter, and in milk). They are absent from cod liver oil. It is therefore obvious that a normal diet would supply sufficient quantities of fatty acids, since they are not significantly altered by cooking processes. Fats of vegetable origin contain linoleic and linolenic acid, while those of animal origin contain linoleic and arachidonic acids.

The biological significance of the essential fatty acids is that they are incorporated into the structural lipids, particularly the phospholipids of cell membranes. When the synthesis of a prostaglandin is required, a phospholipase A₂ hydrolyzes the polyenic fatty acids with 20 carbon atoms derived from phospholipids, and an enzymic system present in the microsomes transforms the polyenic acid into a prostaglandin. In nature there are at least 14 prostaglandins with mutually antagonistic actions. They regulate the cellular content of cyclic AMP and of cyclic GMP. The cellular response to appropriate external stimuli depends upon the ratio of intracellular concentrations of cyclic AMP and cyclic GMP. A shortage of essential fatty acids is very rare, except in extreme starvation.

Therapeutically, polyunsaturated fatty acids are used together with blood fatty acids of lower iodine number in eczema and in coeliac disease, which results in reduced absorption of lipids.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, deficiency of polyunsaturated fatty acids during pregnancy could lead to partial resorption of the foetus, prolongation of the pregnancy, and birth of foetuses with characteristic degeneration of the tail [1, 2, 3].

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* * * * *

Para-amino-benzoic acid or PABA

(MW 137.14)

PABA is a constituent of folic acid, and an essential metabolite for bacterial replication. However, mammals cannot utilize PABA for the synthesis of folates, and therefore it is not a vitamin. The sulphonamides block bacterial replication by acting as antimetabolites of PABA.

Dihydrotachysterol

9,10-seco-ergosta-5,7,22-trien-3 β -ol (MW 398.65)

Dihydrotachysterol is an analogue of vitamin D and a reduction product of both

vitamin D₂ and D₃. It increases calcium levels, mobilizing calcium in bones to a greater extent than calciferol, but it is less effective in preventing rickets. It is therefore used only to increase calcium levels in hypoparathyroidism and in tetany resulting from lack of parathormone. For further information, see calciferol (page 265).

Uridine triphosphate or UTP

salt of uridine-5-triphosphoric acid (MW 484.1)

UTP is a pyrimidine nucleotide derived from carbamyl phosphate, and it is able to limit the synthesis of the nucleotides by inhibition of the enzyme carbamyl-phosphate synthetase. UTP is a donor of high-energy phosphate radicals, utilized in reactions leading to the synthesis of polysaccharides and to the interconversion of galactose-1-phosphate into glucose-1-phosphate. Together with other nucleotides and nucleosides, UTP is used as an energy donor to improve muscular and cardiac contractile force in weakness and muscular atrophy and cardiac imbalance.

We have been unable to find any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. Despite the absence of adverse reports, we believe that their administration should be limited in pregnancy and in women of childbearing age who are likely to conceive.

3. ENZYMES

The following enzymes are used therapeutically:

	Recommendation	Page
Pepsin	NC	274
Extract of gastric mucosa	NC	275
Trypsin	NC	275
Chymotrypsin	NC	275
Total pancreatic extract	NC	276
Pancreatin	NC	276
Kallidinogenase	P	276
Deoxyribonuclease	NC	277
Lipocaic	NC	278
Aspergillase	NC	278
Streptokinase	NC	278
Neuramide	NC	279
Lysozyme	NC	279
Hyaluronidase	NC	280
Thiomucase	NC	281
Bromelains	NC	281

None of these enzymes is contra-indicated in pregnancy.

Pepsin

(MW ~36 000)

Not contra-indicated in pregnancy.

Pepsin is an endopeptidase which, in an acid environment, splits proteins into peptones. It is particularly effective in dyspepsia accompanied by gastric hypochylia.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2].

No experimental studies have been described on the use of pepsin in pregnancy in laboratory animals.

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Extract of gastric mucosa

Not contra-indicated in pregnancy.

Extract of gastric mucosa is composed of the total extract of pig gastric mucosa, and contains Castle's intrinsic factor. It is indicated in the treatment of hyperchromic anaemia and in pregnancy.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been described on the use of extract of gastric mucosa in pregnancy in laboratory animals.

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Trypsin

(MW ~ 23 700)

Not contra-indicated in pregnancy.

Trypsin is a proteolytic enzyme, obtained from ox bile, which splits proteins directly and does not require any specific cofactor. It has a very limited specificity, and also acts on mucine proteins. It can cause anaphylactic shock. Trypsin is used locally, particularly in the treatment of necrotic wounds, ulcers, abscesses, empyema, fistulas, and for the liquefaction of coagulated blood and of exudates which have not reached the stage of becoming fibrous tissue.

Trypsin given parenterally is used in the therapy of acute nonspecific pelvic inflammation, thrombophlebitis of pregnancy, and post-operatively in inflammatory complication of tears caused by birth and episiotomy. The role of trypsin on such cases is solely to complement other therapeutic substances. There have been no reports of harmful effects on the human foetus, the mother, or the pregnancy [1, 2], and the manufacturers concur with this view [3].

No experimental studies have been described on the use of trypsin in pregnancy in laboratory animals.

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Chymotrypsin

Chymocyclar, Chymoral, Chymar, Deanase DC (MW ~ 25 000)

Not contra-indicated in pregnancy.

Chymotrypsin is an enzyme obtained in crystalline form from the pancreas

of mammals by aqueous acid extraction of the proenzyme chymotrypsinogen, and successive conversion by means of trypsin into chymotrypsin. In association with trypsin, chymotrypsin is used as an anti-inflammatory (see page 183).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of chymotrypsin in pregnancy in laboratory animals, and the manufacturers have confirmed this [1].

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[1] Comunicazione personale della Ditta Italfarmaco - Milano.

Total pancreatic extract

Not contra-indicated in pregnancy.

The lyophilized total extract of pancreas has proteolytic activity, and is an aminolytic and lipolytic. It is used as an aid to digestion.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of total pancreatic extract in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta UCB-Smit - Torino.

Pancreatin

Not contra-indicated in pregnancy.

Pancreatin constitutes the total extract of pancreas and possesses an enzymatic—digestive action.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1]. They stress that this substance, which is not absorbed from the intestine, does not appear to cross the placental barrier.

No experimental studies have been described on the use of pancreatin in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta Kali-Chemiopharma - Hanover.

Kallidinogenase

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Kallidinogenase is a proteolytic enzyme present in pancreatic secretions, the saliva, and in other physiological fluids, including blood and urine. Kallidinogenase acts by activating the transformation of kallikreinogen to the corresponding kinins, bradykinin and kallikrein. The plasma kinins possess numerous pharmacological actions. Even at very low doses, they cause vasodilatation, increase capillary permeability with consequent oedema, produce pain by stimulation of nerve terminals, and contraction or relaxation of various types of extravascular smooth muscle. The isolated rat uterus is very sensitive to the contractile action of the kinins, at the extremely low dose of 10^{-10} g/ml. Kallidinogenase has been used for many years with doubtful effect in vasospastic conditions.

Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, kallidinogenase should be used with care because of its pharmacological effects, and on the basis of experimental data.

In the rat, the kallikrein—kinin system prolonged the duration of pregnancy and parturition [1]. An intraperitoneal dose of 20 IU from the 19th to the 22nd day of pregnancy prolonged gestation, increased the duration of parturition, and caused 100% neonatal mortality [1].

Bibliography

- [1] Senior J.: *The Kallikrein-kinin-system and parturition in the rat* - in *Kininogenases-Kallikrein* - 2nd International Symposium - Mainz 29/11/1974 - Schattner Ed. - Stuttgart, 1975.

Deoxyribonuclease

(MW ~ 62 000)

Not contra-indicated in pregnancy.

Deoxyribonuclease is an enzyme extracted from bovine pancreas which depolymerizes DNA to mononucleotides. DNA, which is normally present only in cellular nuclei, is released in the tissues after necrosis, initiates an inflammatory reaction, and increases the viscosity of exudates. Deoxyribonuclease reduces free DNA but not nuclear DNA, into smaller molecules, transforming fibrinous or purulent exudates into more fluid and reabsorbable materials, resolving oedema, and facilitating the penetration of antibacterial chemotherapeutic agents into necrotic foci. The enzyme can also depolymerize tumoral DNA. The enzyme extract available commercially is free from antigenic action, and proteolytic activity. It is used locally and systemically in the therapy of ulceration and of superficial abscesses. It is also used to treat pulmonary abscesses, sinusitis, purulent cystitis, adhesions, mastitis, and intrathecally for meningitis. In oncology, deoxyribonuclease has a synergistic action with chemotherapeutic drugs and with ionizing radiation.

No contra-indications exist to the use of deoxyribonuclease in pregnancy [1, 2, 3].

No experimental studies have been described on the use of deoxyribonuclease in pregnancy in laboratory animals.

Bibliography

- [1] Kastrup E.K., Schwach E.H.: *Facts and Comparison* - Facts and Comparison Ed. - St. Louis, 1975.
- [2] Baker C.E.: *Physicians' Desk Reference* - Med. Econ. Co. Ed. - Oradell, 1975.
- [3] *Dictionnaire Vidal* - O.V.P. Ed. - Paris, 1975.

Lipocaic

Not contra-indicated in pregnancy.

The alcoholic extract of bovine pancreas contains a factor, called 'lipocaic', which prevents hepatic steatosis in dogs whose pancreas has been removed. This factor is not linked to insulin. It is believed that it is a proteolytic enzyme complex which releases methionine from foodstuffs, and thus its pharmacological action is identical to that of methionine itself.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of lipocaic in pregnancy in laboratory animals.

Aspergillase or Diastase

Not contra-indicated in pregnancy.

The amylolytic enzymes of *Aspergillus Orizae* are only slightly absorbed from the gastrointestinal tract. They are used in the treatment of digestive disturbances.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. Since neither substance is significantly absorbed, and toxicity is therefore minimal, they are harmless in pregnancy [1].

No experimental studies have been described on the use of aspergillase or diastase in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Rorer - Milano.

Streptokinase

Kabikinase, Streptase, Varidase

Not contra-indicated in pregnancy.

Streptokinase is produced by certain kinds of streptococcus, which initiate the lysis of fibrin. This process includes activation of plasminogen (contained in deposits of fibrin) to the proteolytic enzyme plasmin, which dissolves the exudates or coagulants containing fibrin. The fibrinolytic processes begin with a change in the physical state of the fibrin, which passes from a gel-type solid into solution, and culminates in the fragmentation of the fibrin molecule into many polypeptides. The activity of streptokinase is maximal at pH 7.3–7.6. It is used in the therapy of haematomas, purulent exudates, and for facilitating drainage and the penetration of antibiotics.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

In the mouse, rat, and rabbit, streptokinase had no embryofoetotoxic or teratogenic effects [5, 6]. In the mouse and rat, doses of 5000 and 7500 IU/kg given intravenously or intraperitoneally from the 1st to the 19th and from the 1st to the 21st day of pregnancy respectively had no harmful effects [5]. In the rabbit, intravenous doses of 5000 and 10 000 IU/kg from the 8th to the 16th day of pregnancy produced no malformations [5].

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- [6] Dato Fornito dal Centro Ricerche Sperimentali SOG. - Padova, 1979.

Neuramide

Not contra-indicated in pregnancy.

Neuramide is a solution of denatured proteolytic enzymes, obtained from the glandular striatum of pig stomach. It is used in the therapy of viral neuritis and of tabes dorsalis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of neuramide in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Difa - Caronno Pertusella (VA).

Lysozyme

(MW 15 000)

Not contra-indicated in pregnancy.

Lysozyme is a basic protein composed of a single chain of about 125 amino acids, with a mucopolysaccharidase action. It is present in all mucosae, amniotic fluid, and blood. The biological significance of lysozyme is widespread and of great importance, especially for the natural defence mechanisms. It attacks the polysaccharide cell wall of certain bacteria, stimulates immune processes, and has antireactive, thromboplastinogenic, and antiheparinic actions. During pregnancy, lysozyme increases in maternal blood [1], but to a lesser degree when toxæmia is present [2]. It is also present in foetal blood in somewhat smaller amounts [3], and in amniotic fluid [3], where it constitutes a natural defence both during pregnancy and particularly in labour. Lysozyme has many therapeutic uses, including as a haemostatic, anti-inflammatory, analgesic, and antileucopoenic.

There have been no reports of harmful effects on the foetus, the mother or the pregnancy [2,4] following administration of lysozyme in pregnancy. Administration of 150 mg to the mother did not increase lysozyme concentration in the amniotic fluid [4]. In toxæmia, administration parenterally of doses of 200 mg/day improved the general condition of the mother without undesired side effects [2].

No experimental studies have been described on the use of lysozyme in pregnancy in laboratory animals.

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- [1] Benoliel W.: Riv. Ost. Gin. 3, 117, 1948 (cit. da 2).
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Hyaluronidase

Hyalase, Lasonil, Xylodase (MW ~ 61000)

Not contra-indicated in pregnancy.

Hyaluronidase is an enzyme which depolymerizes and hydrolyses the mucopolysaccharides, in particular hyaluronic acid, a constituent of the basic intercellular substance. It therefore represents a 'diffusing factor' which increases penetration of drugs into the tissues and thus facilitates absorption. This action is exclusively a local one. Hyaluronidase is used to facilitate the subcutaneous administration of solutions, to combat localized oedemas, and to accelerate reabsorption of exudates, provided that no infection is present.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [4,5].

In the chick embryo, administration of hyaluronidase in high doses was teratogenic [1,2]. It caused the complete arrest of development of the trunk, an omphalocephaly, hypertrophy of the spinal cord, and other malformations of

a more localized character such as cardiac atrophy, dilatation of the aortic arch and of the thoracic aorta [1, 2].

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- [4] Colucci G., Franco G.: Clin. Ost. Gin. 38, 148, 1954.
- [5] Pellizzari C.: Riv. It. Gin. 36, 105, 1953.

Thiomucase

Not contra-indicated in pregnancy.

Thiomucase is an enzymatic extract with depolymerizing action on the basic material of connective tissues, particularly on sulphomucine. This effect is accompanied by a reduction in hydrophylic tissues. Thiomucase is therefore used in the treatment of localized oedemas, in states of water retention, and in the after-effects of trauma.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

In the mouse and rabbit, thiomucase was neither embryofoetotoxic nor teratogenic [1]. A dose of 100 TRU/kg given intramuscularly throughout pregnancy was completely innocuous [1].

Bibliography

- [1] Comunicazione personale della Ditta Crinos - Villaguardia (CO).

Bromelains

Ananase forte

Not contra-indicated in pregnancy.

Bromelains is a complex of proteolytic enzymes obtained from *Ananas comosus*. It possesses anti-inflammatory and anti-oedematous actions, which indicates that it should be of use therapeutically in the after-effects of trauma and surgery.

No reports of harmful effects on the human foetus, the mother, or the pregnancy have been found, and bromelains is currently used in obstetrics and gynaecology [1].

No experimental studies have been described on the use of bromelains in pregnancy in laboratory animals.

Bibliography

- [1] Comunicazione personale della Ditta Rorer - Milano.

4. ELEMENTS

The following products which are currently used therapeutically are grouped together in this chapter:

	Recomendation	Page
Calcium camsilate	NC	282
Calcium glubionate	NC	282
Tribasic calcium phosphate	NC	282
Calcium gluconate	NC	282
Sodium methylarsenate	NC	283
Potassium chloride	NC	283
Potassium gluconate	NC	283
Anhydrous potassium citrate	NC	283
Magnesium ascorbate	NC	284
Iodine	C	285
Iodocaseine	C	285
Iodopeptone	C	285
Prolonium iodide	C	285
Iodetenamine	C	285
Methionine methiodide	C	285

With the exception of iodine, the use of which might be dangerous during pregnancy, the other elements do not present particular contra-indication.

Calcium camsilate

(MW 502.68)

Calcium glubionate

calcium lactate gluconate (MW 610.37)

Tribasic calcium phosphate

(MW 310.18)

Calcium gluconate

Sandocal, Chocovite, Calcium-Sandoz (MW 430.42)

Not contra-indicated in pregnancy.

Calcium is one of the most important constituents of the human body, and plays a determining role in the function of nervous and muscular (including

cardiac) tissues and in cellular membranes in general. Calcium is one of the coagulating factors in blood, Calcium requirements (normally about 10 mg/kg) increase in pregnancy, particularly in the second half, to meet foetal needs.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4, 5, 6, 7, 8]. Calcium may safely be administered in the puerperium, and there have never been any reported signs of intolerance in breastfed infants [4]. In 25 patients, administration of calcium preparations at doses of 0.5–3 g/day for 6 weeks during the last trimester temporarily altered lipid absorption [1]. Oral administration of calcium in pregnancy should reach 2 g/day in the last trimester to obtain a satisfactory calcium balance [2].

No experimental studies have been described on the use of calcium in pregnancy in laboratory animals.

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Sodium methylarsenate

(MW 183.91)

Not contra-indicated in pregnancy.

Sodium methylarsenate is an organic arsenic-containing compound, with limited toxicity. It has a 'reconstituting' action as well as being haemopoietic and calcifying.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of sodium methylarsenate in pregnancy in laboratory animals.

Potassium chloride

(MW 74.55)

Potassium gluconate

(MW 234.27)

Anhydrous potassium citrate

(MW 306.41)

Not contra-indicated in pregnancy.

Potassium is the principal intracellular cation. Maintenance of an adequate concentration is conditioned by the structure and functional integrity of the cells. A shortage of potassium in the organism may be a consequence of an excessive loss in the gastrointestinal tract (vomiting or diarrhoea) or from the kidneys (diuretic, glucocorticoid, mineralocorticoid). Potassium deficiency causes morphological and functional changes in skeletal muscle, the myocardium, and the kidneys, and alterations in metabolism of carbohydrates and of protein synthesis. Treatment of such deficiency states should be undertaken with care, because of probable cardiotoxic effects on potassium, particularly when this is accompanied by dehydration. Special attention has to be paid to administration of potassium intravenously and, in the event of a concurrent chloride lack, to repercussions on the acid–base equilibrium. In patients on a low sodium diet, chlorides of potassium should be administered, but not other potassium salts, otherwise, because of effects relating to the permeability of the renal tubular epithelium to various ions, the deficit of potassium and the acid–base equilibrium will not be corrected.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been described on the use of potassium salts in pregnancy in laboratory animals.

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- [1] Ragni N., Cadenelli G.P.: Min. Gin. 83, 728, 1960.

Magnesium ascorbate

(MW 374.36)

Not contra-indicated in pregnancy.

Magnesium ascorbate is one of the most important cations present in the body, not only structurally (bone tissue) but also metabolically (activation of numerous enzyme systems). The concentration of magnesium is strictly related to that of calcium and of potassium, and depends on parathormone and on vitamin D. A deficiency of magnesium may be shown in diabetic acidosis, in primitive hyperaldosteronism, in hepatic cirrhosis, in renal insufficiency, and in treatment with diuretics, and it is manifested by convulsions caused by increased neuromuscular excitability. On the contrary, administration of magnesium causes central sedation and reduced peripheral excitability. These effects are completely antagonized by administration of calcium, which is used to correct magnesium overdosage. Magnesium is used in therapy as an anticonvulsant and in severe toxæmia (pre-eclampsia and eclampsia).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of magnesium in pregnancy in laboratory animals.

Iodine

(MW 162.9)

Iodocaseine

caseine with 7.2% iodine

Iodopeptone or Prolonium iodide

di-iodo-hexamethyldiamino-isopropanol (MW 430.13)

Iodetenamine

iodotrimethyl-aminoethanol hexamethylene tetramine (MW 371.27)

Methionine methiodide

3-amino-3-carboxy-propyl-dimethylsulphonium iodide (MW 277.13)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Iodine is one of the oligo-elements indispensable for homeostasis of the organism and embryonal development. When ingested with food, it is absorbed from the digestive tract in a variable manner, which depends upon the composition of the latter. In the form of iodine, it is excreted in saliva, sweat, milk, and particularly urine. The greater part of circulating iodine is captured in the thyroid, utilized for the synthesis of the thyroid hormones (see thyroxine, page 152), and stored in the form of thyroglobulin. Antithyroid drugs and thyrotropic hormone (see page 153) interfere with these processes (see carbimazole, page 157). On the other hand, iodine exerts a negative feedback on TSH release. This inhibitory effect is more evident in conditions of hyperthyroidism than in euthyroidism, for reasons which are not clear, and is particularly noticeable in foetal life.

During pregnancy, iodine requirement increases from 100 μg to 150 μg per day [1, 2]. Therapeutic administration of iodine is limited to preparation of patients who need to undergo surgery on the thyroid, or as a local disinfectant

for skin and mucosa. It is worth remembering that in some parts of the world where iodine is scarce, it is used in the prevention of goitre caused by hyperthyroidism.

Iodine crosses the placental barrier, and is actively captured by the foetal thyroid, which is more active than that of the mother [3]. It should be emphasized that the iodides are contained in products in current use as expectorants, which can be readily bought without a prescription [4, 5]. In eight cases who had taken iodine-containing expectorants during pregnancy, containing quantities of iodine varying between 12 and 1650 mg, goitre and neonatal hypothyroidism [4] appeared in the infant. A neonate with thyrotoxicosis was born to a patient who had taken an anti-asthma preparation containing 3.6% sodium iodide [5]. Administration of iodine and iodide in pregnancy is strongly contra-indicated because of the consistent appearance of goitre and of hypothyroidism in the foetus, which gives rise to serious problems in the neonatal period (hypothyroidism with cardiac insufficiency, tracheal compression, shock) and during subsequent development (mental retardation to the point of cretinism) [4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21]. Even the execution of a contrastogram during pregnancy with contrast medium containing iodine, such as a bronchogram [16], may alter the mental development of the neonate. Iodine is also cited as one of the drugs which can induce erythrocytopenia [18]. In this case too, there is danger to the foetus.

In the rat, guinea-pig, and rabbit, the effect on reproduction of excess iodine in the diet has been studied. In the rabbit, iodine increased neonatal mortality, while in the rat it caused a prolongation of labour [22].

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5. ANTI-GOUT AND URICOSURIC PREPARATIONS

In the clinical manifestations of hyperuricaemia, drugs may be used which inhibit the biosynthesis of uric acid (allopurinol) or which impede renal reabsorption (probenecid, sulphinpyrazone, isobromindione). In an acute attack of gout, colchicine is indicated because of its anti-inflammatory action on urate deposits. The following drugs are discussed in this chapter:

	Recommendation	Page
Allopurinol	P	288
Probenecid	NC	289
Sulphinpyrazone	NC	289
Colchicine	C	290

While uricosuric products are not contra-indicated in pregnancy, there are certain reservations with regard to allopurinol, while the use of colchicine should be excluded. We believe that there is insufficient information to recommend the use of isobromindione in pregnancy (see page 292).

Allopurinol

Zyloric, 1*H*-pyrazol(3,4-*d*)pyrimidin-4-ol (MW 136.11)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Allopurinol is an antimetabolite of oxypurine and a competitive and non-competitive inhibitor of the enzyme xanthine oxidase, which catalyses the formation of uric acid. Blockage of this catabolic route results in hypoxanthine and xanthine being eliminated in the urine (given their renal clearance) rather than being transformed into uric acid. Allopurinol inhibits the catabolism of 6-mercaptopurine and of azathioprine, and thus augments their effects. It also increases the myelotoxicity of cyclophosphamide.

Allopurinol should be used with care in pregnancy, since it affects the metabolism of purine and pyrimidine, even although there are no specific contra-indications. Care is particularly indicated when treatment is long-term [1,2].

In laboratory animals, allopurinol was neither embryofetotoxic nor teratogenic [1,2].

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Probenecid

Benemid, *p*-(dipropylsulphamyl)benzoic acid (MW 285.36)

Not contra-indicated in pregnancy.

Probenecid is a derivative of benzoic acid, and was synthesized with the aim of reducing renal excretion of penicillins. It was seen that it could also inhibit the tubular reabsorption of many other organic compounds, including uric acid para-amino-salicylic acid, cephalosporins, sulphonamides, bromosulphthalein, para-amino-hippuric acid, and 17-ketosteroids. The salicylates counteract the uricosuric action of probenecid. Probenecid is rapidly absorbed orally, binds strongly to plasma proteins, and is partially metabolized and eliminated in the urine.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3], and the manufacturers concur with this view [4].

No experimental studies have been described on the use of probenecid in pregnancy in laboratory animals.

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Sulphinpyrazone

Anturan,

1,2-diphenyl-3,5-dioxo-4-(2-phenyl-sulphonyl-ethyl)-pyrazolidine
(MW 404.48)

Not contra-indicated in pregnancy.

Phenylbutazone has a slight uricosuric effect, probably indirect, and is linked to some catabolite which reduces tubular reabsorption of uric acid. Sulphinpyrazone is in fact a metabolite of phenylbutazone, and is particularly active as a uricosuric, but without any anti-inflammatory, analgesic, or antipyretic actions. However, it retains the property of being able to displace certain drugs which bind to plasma proteins, including the sulphonamides (see phenylbutazone, page 192). Sulphinpyrazone also possesses an action against

platelet aggregation, which is mediated by means of blockage of ADP and serotonin release. It is well absorbed orally, binds almost completely to plasma proteins, and is slowly eliminated intact in the urine. Its toxicity is similar to that of phenylbutazone, and manifests itself in the digestive tract, the blood-forming organs, and the hepatic and renal parenchyma.

No reports have been found on harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3], and the manufacturers concur with this view [4].

No experimental studies have been described on the use of sulphinpyrazone in pregnancy in laboratory animals.

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Colchicine

(MW 399.43)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C				

Contra-indicated in pregnancy.

Colchicine is an alkaloid from *Colchicum autumnale*, and has been used in the treatment of gout for more than two centuries. Its two most important pharmacological properties both appear to occur as the result of a single mechanism of action: blockage of the cellular inflammatory reaction (leucocyte) at the level of synovial precipitation of urates, and blockage of mitosis during the metaphase. This occurs because colchicine can bind to the proteins of the cellular microtubules, preventing their function. It has been seen that colchicine reduces the release of granules containing histamine in the mastocytes, of insulin from β cells, and of the movement of granules of melanin in the melanocytes and the neutrophils. Colchicine does not alter uric acid metabolism (uricuria, uricaemia, urate pool), but it has a central depressant effect, as well as being a sympathomimetic and a motor stimulant of gastrointestinal smooth muscle.

Colchicine is rapidly absorbed orally, does not remain in the blood, but is directly attached to parenchyma (except in striated muscle), and in particular to leucocytes. It is deacetylated in the liver and eliminated with the bile. Colchicine can cause gastrointestinal disturbances (nausea, vomiting, diarrhoea, abdominal

pain) and, in prolonged therapy, alopecia and depression of bone marrow. It is used to treat and prevent acute attacks of gout, and also as an antimetabolic in oncology.

Colchicine is thought to be both abortive and teratogenic in humans [1, 2, 3, 4, 5, 6, 22].

In the mouse, rat, rabbit, chick embryo, amphibians, and hamster, colchicine was teratogenic [8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20]. In the mouse, administration of colchicine at various stages of pregnancy caused teratogenic effects [20]. It also gave rise to abortions [16, 17, 18]. Subcutaneous doses of 0.5–2.5 mg/kg from the 7th to the 10th day or from the 11th to the 14th day of pregnancy were foetotoxic and teratogenic, causing malformations of the limbs and tail, and cleft palate [9].

In the rat, administration of colchicine in pregnancy caused abortion [18]. Parenteral doses of 0.6 mg/kg in a single administration from the 6th to the 14th day of pregnancy were foetotoxic and teratogenic, producing malformations of limbs and tail [8].

Subcutaneous doses of 2 mg/kg in the rabbit on the 14th day of pregnancy were embryotoxic, causing death of the embryo [10]. Fertilization of rabbits with sperm suspended in a solution containing 0.1% colchicine gave rise to the formation of otocephaly and microcephaly in two offspring out of 23 [15]. Doses of 0.1–5 mg/kg after the 9th day of gestation were foetotoxic [12]. Doses of 0.1–0.5 mg/kg caused gastroschisis in a small percentage of neonates, and failure of closure of the neural duct [12].

In chick embryo injected with colchicine in the 48th hour of incubation, there was anuria, celosomia, syndactyly, ectrodactyly, scoliosis, lordosis, strophosomus, and ectromelus hemimelus [14]. Addition of colchicine to the water surrounding amphibians caused cyclopia [19].

Intravenous doses of 10–50 mg/kg given to the hamster on the 8th day of gestation were teratogenic, causing exencephaly, alterations of the eye, and gastroschisis [11].

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* * * * *

Isobromindione

5-bromo-2-phenyl-indan-1,3-dione (MW 301.14)

Isobromindione is a derivative of indandione, with no anticoagulant effects. It blocks reabsorption of uric acid in the proximal tubule.

We have been unable to find any information on the use of this drug in pregnancy, either in the literature or from the manufacturers. Despite the absence of adverse reports, we advise against its use in pregnancy or in women of childbearing age who are likely to conceive.

6. CHELATING AGENTS, ANTIDOTES, ION EXCHANGE RESINS

It is possible to use many specific drugs in cases of poisoning. For example, in poisoning by heavy metals, there are chelating agents: EDTA (sodium acetate), which is indicated in lead poisoning, dimercaprol, used in poisoning by mercury, cadmium, etc., desferrioxamine, indicated in poisoning with iron. The latter is used in haemosiderosis and haemochromatosis. There are also specific antidotes in other fields of poisoning, such as pralidoxime for phosphoric esters or nalorphine for morphine. We have also included here those ion exchange resins which are used in therapy; cholestyramine to remove cholesterol and polystyrene sulphonate for potassium. The following substances are discussed in this chapter:

	Recommendation	Page
Sodium edetate	P	293
Dimercaprol	P	294
Desferrioxamine	P	295
Disulfiram	P	296
Trometamol	P	297
Glucuronolactone	NC	298
Pralidoxime methylsulphate	NC	298
Nalorphine	NC	298
Protamine sulphate	NC	299
Polystyrene sodium sulphonate	NC	299

The use of some of the above requires care in pregnancy, because of their mechanism of action. We believe that insufficient evidence of safety exists to recommend the use of toluidine blue, sodium thiosulphate, and cholestyramine (see page 300) in pregnancy.

Sodium edetate or EDTA

ethylamine diamine tetra-acetate (MW 374.28)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P				

To be used with care in pregnancy.

Sodium edetate is used principally in lead poisoning. Its mechanism of action is based upon the displacement of the lead by the calcium in edetic acid.

The latter then forms an edetate of lead, which is eliminated via the kidneys. Sodium edetate is also used in the treatment of poisoning by other heavy metals such as plutonium, while it is of some use in arsenic and mercury poisoning also.

Transplacental passage of EDTA has been demonstrated, although because of its structure, it does not pass into maternal or foetal cells [1]. Its use in pregnancy should be cautious, because its safety has not been sufficiently proved [2, 3].

In the rat, EDTA was embryofetotoxic and teratogenic [4, 5]. Administration at doses of 20 mg and 40 mg during embryogenesis caused defects in the tail and polydactyly [4]. Administration at 2–3% in the diet of rats after the 6th day of gestation caused cleft palate, malformations of the nervous system, and ocular and skeletal anomalies [5].

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Dimercaprol

2,3-dimercapto-1-propanol (MW 124.21)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P	P	P		
Chronic	P	P	P		

To be used with care in pregnancy.

Dimercaprol is a thiol compound which competes with the arsenicals for tissue sulphhydryl groups. In fact, the arsenicals are chelated by dimercaprol, and transformed into nontoxic substances. Dimercaprol thus protects against the toxic effects of heavy metals, particularly mercury and cadmium. It also inhibits certain enzyme systems (catalase, peroxidase, carbonic anhydrase, cytochrome oxidase) which are activated by metallic ions. It potentiates the hypotensive action of bradykinin by inhibition of zinc-dependent carboxypeptidase, and also inactivates, at least *in vitro*, insulin by reducing the disulphide bridges which are essential for its activity. Dimercaprol at low doses has a hypertensive action resulting from arteriolar vasoconstriction, and it can cause a series of side effects, including nausea, mucositis, abdominal pain, anxiety, etc. It is an effective antidote to poisoning by antimony, bismuth, mercury, gold, chromium, and nickel, but is relatively ineffective in lead poisoning.

Dimercaprol crosses the placental barrier [1]. Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2, 3, 4, 5], we believe that dimercaprol should be used with care in pregnancy because of its mechanism of action. It may, in fact, cause haemolysis of red cells in the neonate if there is a deficiency of glucose-6-phosphate dehydrogenase [6].

In laboratory animals, administration of dimercaprol in pregnancy was teratogenic [8].

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Desferrioxamine

Desferal,

N-(5-(3-((5-aminopentyl)hydroxycarbamoyl)propionamido)pentyl)-3-((5-(*N*-hydroxyacetamido)pentyl)carbamoyl)propionohydroxamic acid (MW 560.71)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P	P	P		
Chronic	P	P	P		

To be used with care in pregnancy.

Desferrioxamine is a chelator of iron, and is obtained by extraction from *Streptococcus pilosus*. It is highly specific for this metal. Desferrioxamine can remove iron from ferritin and from haemosiderin, but does not remove a significant amount from transferrin. It is also unable to chelate iron in respiratory pigment. Desferrioxamine is very slightly absorbed orally, and is usually administered intramuscularly in haemosiderosis, haemochromatosis, acute iron poisoning, and thalassaemia. It is used diagnostically to reveal iron accumulation. The desferal test, combined with a fixed iron load, was carried out in 44 pregnant women with no maternal or foetal side effects [1].

No embryofoetotoxic or teratogenic effects have been described following the use of desferrioxamine in pregnancy [1]. However, because of its mechanism of action, the drug should be used with care.

In the rat, desferrioxamine at high doses in the early part of gestation caused abortion [2]. Some authors also found that it was teratogenic [3]. The drug was administered at doses of 10–15–20 mg/day from the 1st to the 9th day of pregnancy, or at doses of 20 mg/day from the 10th to the 15th or from the 16th to the 19th day of pregnancy. There was an increase in the number of abortions in the group treated with 10 mg from the 1st to the 9th day. This percentage was doubled in animals treated with 15 mg/day and was increased still more in the group treated for the same period with 20 mg/day. A very low incidence of abortions was observed in the last two groups, even although maximal doses were used [2]. Desferrioxamine was not found to be teratogenic in this study [2]. Absence of direct effects on the embryo could be explained by the fact that desferrioxamine did not cross the placental barrier in the rat, or did so in very small amounts. Even although the placenta was not properly formed at the time at which the drug was administered, there could be some factor present which hindered the drug from passing directly to the embryo [2].

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Disulfiram

Antabuse, bis(diethylthiocarbamyl)disulphide (MW 296.54)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P	P	P		
Chronic	P	P	P		

To be used with care in pregnancy.

Disulfiram is an antioxidant which blocks the hepatic transformation of ethanol into acetaldehyde. Normally, aldehyde dehydrogenase catalyses the further oxidation of acetaldehyde. Disulfiram competes with DPN for active sites on aldehyde dehydrogenase, inducing a rapid and significant increase in acetaldehyde following ingestion of ethyl alcohol. The effects produced include vasodilatation, headache, hypotension, nausea, vomiting, perspiration, vertigo, shock, and even myocardial infarction if ischaemic heart disease is present. The action of disulfiram is probably more complex because of its antioxidant effects on other metabolic processes. It is used to treat chronic alcoholism.

Disulfiram should be used with care in pregnancy [1,2]. Other authors believe that it should be contra-indicated in the first trimester, although there is no evidence of harmful effects on the foetus [3].

No experimental studies have been described on the use of disulfiram in pregnancy in laboratory animals.

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Trometamol or THAM

tris-(hydroxymethyl)-aminomethane (MW 121.14)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Trometamol is a buffer, and is able to neutralize acidosis both intra- and extracellularly, although a large percentage is not ionized at normal blood pH and passes into the cells. This molecule also has a metabolic action which produces hypoglycaemia and which is analogous in certain respects to that of insulin. Trometamol activates gluconeogenesis, inhibits glycogenolysis, activates hexokinase, and produces both myotropic and negative inotropic effects on the heart. It is used in the therapy of metabolic (diabetes and severe burns) or respiratory (acute or chronic pulmonary hypoventilation) acidosis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, trometamol should be used with care because of its metabolic effects [3], and the manufacturers concur with this view [1]. In neonatal metabolic disturbances, trometamol is used to correct acidosis, but it can cause an increase in pH and a significant diminution in $p\text{CO}_2$ in arterial blood, with consequent compensatory pulmonary hypoventilation. In such cases, it is often necessary to apply immediate artificial ventilation [2].

No experimental studies have been described on the use of trometamol in pregnancy in laboratory animals.

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Glucuronolactone

glucuronic acid lactone (MW 176.12)

Not contra-indicated in pregnancy.

Glucuronolactone has a detoxifying action in that it facilitates the hepatic synthesis of glucuronic acid, which is its precursor. It is used in the therapy of endogenous and exogenous intoxication, including alcoholism.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1].

No experimental studies have been described on the use of glucuronolactone in pregnancy in laboratory animals.

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Pralidoxime methylsulphate

1-*N*-methyl-2-hydroximinomethyl-pyridine methylsulphate (MW 232.28)

Not contra-indicated in pregnancy.

Pralidoxime is a reactivator of cholinesterase, and is used in poisoning with phosphoric esters. Pralidoxime is in fact able to displace an atom of phosphorus from the complex with the enzyme because it has a greater affinity for this element. Its action diminishes with time, however, and its therapeutic efficacy is reduced.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the quail, rat, mouse, and hamster, pralidoxime was neither embryo-foetotoxic nor teratogenic, and actually protected against the teratogenic effects of parathion [1,3] and bidrin [2]. In the pregnant rat, mouse, and hamster, treated first with parathion and then 3 hours later with 1 mg/kg intraperitoneally of pralidoxime methylsulphate, there was a reduction in the incidence of teratogenic effects. The level of teratogenicity remained high, however, even although the treatment was carried out at the time of attachment of the ovum [3].

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Nalorphine

N-allyl-normorphine hydrobromide (MW 311.37)

Not contra-indicated in pregnancy.

Nalorphine is a semi-synthetic derivative of morphine, and can prevent many of the actions of morphine in man and animals. The appearance of a

withdrawal syndrome on administration of nalorphine to patients who are physically dependent on morphine constitutes its most important action. Small doses (1–3 mg) cause the appearance of an acute withdrawal syndrome which is qualitatively similar to that caused by the sudden cessation of morphine. The mechanism of action of nalorphine is not known.

Nalorphine crosses the placental barrier [4, 5]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4, 5, 6, 8].

In the hamster, nalorphine was neither embryofoetotoxic nor teratogenic [7]. Subcutaneous doses of 92–312 mg/kg throughout pregnancy were not teratogenic. Doses of 245 mg/kg, 20–30 minutes before injection of 232 mg/kg morphine or 129 mg/kg hydromorphone or 90 mg/kg methadone, blocked the teratogenic effects of these drugs [7].

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Protamine sulphate

Not contra-indicated in pregnancy.

Protamine sulphate is a basic protein, and combines with heparin or acid mucopolysaccharide to form a stable, biologically inactive complex. Administered intravenously, it is used as an antidote in severe haemorrhage caused by heparin overdose. Protamine depresses the contraction of vasal and cardiac smooth muscle and is therefore able to induce hypotension, bradycardia, and peripheral vasodilatation. It also has slight anticoagulant action, and thus may interfere with the formation of thromboplastin.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

No experimental studies have been described on the use of protamine in pregnancy in laboratory animals.

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Polystyrene sodium sulphonate

Not contra-indicated in pregnancy.

Polystyrene sodium sulphonate is an ion exchange resin, a macromolecular synthetic product which contains both acid and basic groups. Although insoluble, ion exchange resins are ionized in solution, and the cations or anions from the resin can exchange with ions from the solution. Sodium polystyrene sulphonate, which is often used in association with diuretics, including mercurials, can remove potassium from extracellular fluids and from plasma, particularly in acute renal insufficiency.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4, 5].

No experimental studies have been described on the use of polystyrene sodium sulphonate in pregnancy in laboratory animals.

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Toluidine blue

(MW 305.83)

Toluidine blue is a colouring agent which neutralizes heparin, forming a stable complex with the latter. It is used as an antihaemorrhagic agent, and particularly as an antidote to heparin overdose, but the side effects (methaemoglobinaemia) and its slow onset of action have caused it to be superseded.

Sodium thiosulphate

(MW 248.2)

Thiosulphate or hyposulphite of sodium is used mainly as an antidote to cyanide poisoning, in which it is transformed into sulphocyanic acid.

Cholestyramine

Cholestyramine is the hydrochloride of a strongly basic ion exchange resin which can bind to bile acids, forming an insoluble complex which can leave the entero-hepatic circulation and is eliminated in the faeces. Cholestyramine is administered orally in obstructive jaundice, in hypercholesterolaemia, in hyperlipoproteinaemia, in porphyria, and in diarrhoea in patients who have undergone intestinal bypass.

Cholestyramine has been used in the therapy of idiopathic jaundice in pregnancy (hepatogestosis) in the second and third trimesters. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of cholestyramine in pregnancy in laboratory animals.

We have been unable to find any information on clinical studies or experimental research on these drugs, either in the literature or from the manufacturers. although there have been no reports of adverse effects, we believe that these drugs should not be administered in pregnancy or in women of childbearing age who are likely to conceive.

Part 9

Antibiotics and chemotherapeutic substances

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1. ANTIBIOTICS

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1.1 Penicillin

Penicillin was the first and the most widely used antibiotic. From the preparations obtained from fermentation, there are now available semi-synthetic compounds with a wider antibacterial spectrum, resistance to gastric acids, and resistance to degradation by beta-lactamase enzyme (penicillinase) produced by some bacteria. The following penicillins are discussed here:

	Recommendation	Page
<i>Penicillinase sensitive</i>		
Amoxicillin	NC	304
Ampicillin	NC	305
Epicillin	NC	306
Benzatin benzylpenicillin	NC	307
Benzylpenicillin	NC	307
Sodium carbenicillin	NC	309
Potassium etacillin	NC	310
Potassium pheneticillin	NC	310
Phenoxymethylpenicillin	NC	311
Penetacillin	NC	311
Potassium propicillin	NC	312
<i>Penicillinase resistant</i>		
Cloxacillin sodium	NC	312
Dicloxacillin sodium	NC	313
Flucloxacillin	NC	314
Metampicillin	NC	314
Methicillin sodium	NC	314
Oxacillin sodium	NC	315

No penicillin is contra-indicated in pregnancy. There is inadequate information available, however, on the effects of some of them on the foetus.

Penicillinase sensitive

Amoxicillin

Amoxil,

6-(D-(-)- α -amino-para-hydroxyphenylacetamido)penicillanic acid
(MW 419.6)

Not contra-indicated in pregnancy.

Amoxicillin is a semi-synthetic penicillin, penicillinase sensitive, and is actively absorbed following oral administration. Its pharmacological characteristics are almost identical to those of ampicillin, to which it is structurally similar. It differs from the latter in that higher blood concentrations may be reached in proportion to the dose, when given orally.

Amoxicillin crosses the placental barrier [13]. Experience of clinical use of this drug was scarce until a few years ago, and care was advised when using it in pregnancy [1, 2]. More recent studies have shown no harmful effects on the offspring [8, 9, 11, 12, 13, 14]. Amoxycillin was used in 11 cases of cystitis or cystopyelitis in pregnancy at a dose of 750 mg/day with no foetal side effects [8].

In laboratory animals, studies on the embryofetotoxicity of amoxicillin have given controversial results. Some authors have claimed that the drug is embryotoxic [3], while others believe that it has no embryotoxic or teratogenic effects [5], even in association with dicloxacillin [6]. In the rat and mouse, doses of 150–300–1200 mg/kg from the 6th to the 15th day of pregnancy had no harmful effects, even at the highest dose [5]. In the rat, oral administration at a dose of 100–200 mg/kg/day throughout pregnancy produced no teratogenic effects [10]. In the rabbit, oral doses of 100 mg/kg together with 100 mg/kg dicloxacillin from the 6th to the 18th day of pregnancy were not teratogenic [6].

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Ampicillin

Amfipen, Ampiclox, Magnapen, Penbritin, Pentrexyl, Vidopen,
6-(D-(-)-aminophenylacetamido)-penicillanic acid (MW 349.42)

Not contra-indicated in pregnancy.

Ampicillin is a semi-synthetic penicillin which is noted for its resistance to gastric acids. It is thus active orally. It has a wide spectrum of action, and is active against Gram-negative bacteria. Ampicillin is eliminated in the bile.

Ampicillin crosses the placental barrier, and reaches concentrations in foetal blood and amniotic fluid which are lower than those in maternal blood [1, 8, 9, 10, 11, 12, 13, 14, 15]. After oral administration of 750 mg between the 10th and 16th week of pregnancy, maximum plasma concentrations were reached in 1 hour and in the placenta after 3 hours. In embryonic tissue, the concentration of ampicillin remained low compared to maternal plasma [14]. Ampicillin was concentrated in amniotic fluid at particularly high levels compared to those of cord blood, probably because of its excretion in the urine [8]. It would appear that at the usual doses a therapeutic concentration was almost always reached in the amniotic fluid, but not in foetal blood [8]. Sixty minutes after intramuscular administration to the mother, the amount in foetal plasma was 1–2 mg [19].

Ampicillin is not contra-indicated in pregnancy, provided that there is no penicillin hypersensitivity [2, 16, 17, 19, 25]. It is used in urinary tract infections [3, 18]. The producers also maintain that its use in pregnancy is innocuous to the mother and the foetus [4]. Administration of 1200 mg ampicillin in a single dose at the end of pregnancy for prophylaxis of amniotic infection caused no harmful effects in the foetus [19]. Administration in the last trimester induced a diminution in urinary oestriol [20, 21, 22, 23, 24] because of loss of steroids in the faeces, and because of inhibition of conjugated oestriol hydrolysis in the intestinal tract [24]. There were no changes in plasma oestradiol, oestriol, or cortisol [20].

In the rat, ampicillin was teratogenic [5, 6, 7]. Intraperitoneal doses of 2.8–3 g/kg from the 10th to the 15th day of pregnancy were both embryofoetotoxic and teratogenic [6, 7].

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Epicillin

(D-amino-(1,4-cyclohexadienyl)-methyl)-penicillin (MW 351.4)

Not contra-indicated in pregnancy.

Epicillin is a semi-synthetic penicillin with a similar spectrum of activity to that of ampicillin, although it is also active against *Pseudomonas aeruginosa*. Epicillin is rapidly absorbed from the digestive tract, binds to plasma proteins to the extent of 10–30%, and has a plasma half life of several hours. Its side effects are similar to those of ampicillin.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, mouse, and rabbit, epicillin was neither embryofoetotoxic nor teratogenic [1]. In the rat, oral administration of epicillin at doses of 500–1000–2500 mg/kg and subcutaneous administration of 100–300 mg/kg throughout pregnancy did not increase the incidence of foetal resorptions or mortality. Foetal weight remained normal, and no malformations were observed [1]. In the mouse, similar oral doses throughout pregnancy were likewise without harmful effects [1]. In the rabbit, the same doses given orally, and intravenous doses of 100–300 mg/kg throughout pregnancy, were innocuous [1]. Oral doses of 500 mg/kg and subcutaneous doses of 200 mg/kg from the 7th to the 15th day of pregnancy were without harmful effects [2].

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Benzatin benzylpenicillin

N,N'-dibenzylethylenediamine dipenicillin G (MW 909.11)

Not contra-indicated in pregnancy.

Benzatin benzylpenicillin is a salt which is obtained by combination of two molecules of benzylpenicillin with one molecule of dibenzylethylenediamine. It is used when slow absorption and prolonged maintenance of adequate plasma concentrations are required.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

Benzatin benzylpenicillin was not teratogenic in laboratory animals [5].

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Benzylpenicillin or sodium penicillin G

Bicillin, Crystapen G, Penidural-AP, Tripolpen (MW 356.4)

Not contra-indicated in pregnancy.

Penicillin G is a natural antibiotic which, in the form of its sodium or potassium salts, was the first of its type. It is active on some Gram-positive and some Gram-negative bacteria such as staphylococci, streptococci, gonococci, coryne bacteria, and treponema. Each species of bacteria is able eventually to produce more penicillin-resistant strains by developing the capacity to synthesize penicillinase, the enzyme which inactivates penicillin by opening the lactam ring.

Penicillin acts by blocking a step in protein synthesis which leads to the formation of the glycoprotein macromolecule necessary for providing rigidity to the bacterial cell wall. When this is lacking, the bacteria swell up and die because of elevated intracellular osmotic pressure.

Penicillin G is destroyed by gastric acid, and therefore has to be administered intramuscularly. The combination with procaine or benzatin slows absorption and produces a longer duration of action. Elimination occurs mainly through the urine (renal tubular secretion) and is much reduced in premature infants, whose renal function is still relatively inefficient.

Penicillin G crosses the placental barrier, and reaches therapeutic concentrations in foetal blood [1, 2, 3, 17, 24], approximately 25–75% those of maternal blood [17, 18, 19]. Blood levels in the neonate can be as high as 50% of those in the mother [20]. In amniotic fluid, penicillin G concentrations may even surpass those of maternal plasma for long periods [5].

Penicillin G has been widely used in obstetrics, including the treatment of congenital syphilis, without causing any embryofoetotoxic or teratogenic effects. Our own clinical experience is similar. Administration of penicillin may, occasionally, give rise to shock with consequent abortion [6, 7, 9, 10]. Two cases of threatened abortion in patients treated with penicillin were considered to be due to shock following its administration; the foetuses in these cases were, however, unharmed [6]. Other authors [7, 8] have reported that the numbers of abortions and threatened abortions in pregnant women treated with penicillin G were greater than those in women on alternative forms of therapy. One foetal death has been reported [9] as a result of shock to the mother following antibiotic administration.

Three cases of malformations were reported after treatment with penicillin in the first trimester [10]. Conclusions regarding a possible teratogenic action of penicillin could not, however, be verified in a much larger number of clinical cases throughout the world. Overall, therefore, it can be concluded that penicillin does not have harmful side effects when administered in pregnancy [2, 20, 21, 25, 26, 27, 28, 29].

Penicillin G passes into breast milk [11]. After administration of 100 000 U penicillin a concentration of 0.015–0.06 U/ml was found in the milk (2–20%), while the corresponding serum levels were 0.5–2 U/ml [11]. Intravenous penicillin given to cows in such a way as to produce a constant blood level passed into the milk to the extent of 10–20% of plasma levels [22].

In the rat, rabbit, and macaque mulatto, penicillin was neither embryo-foetotoxic nor teratogenic [12, 13, 15, 16]. In the mouse it was embryofoetotoxic [14]. In the rat, doses of 10 000 U throughout pregnancy were not teratogenic [13]. In the mouse, doses of 50–500 U subcutaneously on the 14th day of pregnancy caused a reduction in foetal weight gain [14]. In the rabbit, doses of 10–100 mg/kg throughout pregnancy were without harmful effects [15]. At doses of 50–200–500 mg/kg for 10 days during pregnancy, penicillin was toxic to the mother but not teratogenic [16]. Doses of 10–100 mg/kg caused abortions but not malformations, and the abortive effect could be correlated with the state of maternal toxicity rather than as a result of a direct action of penicillin on the embryo [15].

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Sodium carbenicillin or carindacillin

Pyopen, sodium (α -carboxybenzyl) penicillin (MW 422.4)

Not contra-indicated in pregnancy.

Carbenicillin is a semi-synthetic penicillin, active against *Pseudomonas pyocianea*. It is administered orally. For further information, see sodium penicillin G (page 307).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, some authors [2,3] state that carbenicillin should be used with care in pregnancy because its safety has not been sufficiently proved. Carbenicillin can be used in patients with hepatic insufficiency, but greater care is required in renal insufficiency [1].

Carbenicillin passes into breast milk, where it reaches low concentrations at therapeutic doses [9].

In the rabbit, rat, and mouse, carbenicillin was neither embryofoetotoxic nor teratogenic [4,5,6], nor did it affect the mother or the course of pregnancy [5]. Some authors, however, have expressed reservations on this [7,8]. In the rabbit, for example, they maintain that no conclusions can be drawn regarding the teratogenicity of carbenicillin [7]. The drug does appear to be toxic to the pregnant animal at doses of only 100 mg/kg/day. This is related not so much to the direct action on the pregnancy, as to changes induced in the intestinal flora [8], and foetal malformations were not reported [7,8]. There was no abortive action [4].

In the rat, doses of 500–1000 mg/kg before and for the first 3 days of pregnancy were neither embryofetotoxic nor teratogenic [4]. Subcutaneous doses of 100–500 mg/kg from the 6th to the 15th day of pregnancy had no harmful side effects in the mother or the foetus [5].

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Potassium etacillin

6-(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)penicillinanic acid potassium salt (MW 427.6)

Not contra-indicated in pregnancy.

Etacillin is a semi-synthetic penicillin with a wide spectrum of activity, but it is not resistant to penicillinase. It is degraded to ampicillin, and possesses the latter's characteristics (see ampicillin, page 305).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In laboratory animals etacillin was not teratogenic [1, 2, 3, 4]. In the rabbit, doses of 50–200–500 mg/kg were without harmful effects [4].

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Potassium pheneticillin

6-(α -phenoxypropionamido)-penicillanic acid potassium salt (MW 402.5)

Not contra-indicated in pregnancy.

Pheneticillin is a semi-synthetic penicillin which is acid resistant, and thus

may be administered orally. Its spectrum of activity is similar to that of penicillin G, of which it represents the orally active form. For further information, see penicillin G (page 307).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 4].

No experimental studies have been described on the use of pheneticillin in pregnancy in laboratory animals.

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Phenoxymethylpenicillin or penicillin V

Apsin VK, CVK, Distaquaine V-K, Crystapen V, Icipen, Tonsillin, V-Cil-K (MW 350.4)

Not contra-indicated in pregnancy.

Penicillin V is a semi-synthetic penicillin which is acid resistant and penicillinase sensitive. After oral administration, it is not inactivated by gastric acids, but is only partially absorbed from the gastrointestinal tract. Maximum plasma concentrations are less than those obtained with other oral penicillins, but antibacterial activity is greater, and similar to that of penicillin G (see page 307).

The transplacental passage of penicillin V has been demonstrated [1, 8]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2, 3, 4, 5].

In laboratory animals, administration of penicillin V in pregnancy was neither embryofoetotoxic nor teratogenic [6].

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Penetacillin

benzylpenicillin diethylamionethyl ester hydriodide (MW 561.5)

Not contra-indicated in pregnancy.

Penetacillin is a semi-synthetic antibiotic which has been prepared with the aim of producing a particularly high concentration in the lungs.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of penetacillin in pregnancy in laboratory animals.

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Potassium propicillin

α -phenoxy-*n*-propylpenicillinate potassium (MW 416.5)

Not contra-indicated in pregnancy.

Propicillin is an acid resistant semi-synthetic penicillin which can be administered orally.

Transplacental passage of propicillin has been demonstrated in man [6]. The amount of the drug found in the foetus is directly proportional to and dependent on the dose administered to the mother, but is considerably less [1]. No reports have been found of harmful effects on the human foetus, the mother or the pregnancy [2, 3, 6].

In laboratory animals, propicillin was neither embryofoetotoxic nor teratogenic [4, 5].

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Penicillinase resistant

Cloxacillin sodium

Ampiclox, Orbenin, sodium salt of

6-(3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamido)-penicillanic acid (MW 475.9)

Not contra-indicated in pregnancy.

Cloxacillin is a semi-synthetic penicillin which is active orally, and has a narrower spectrum of activity than penicillin. It is, however, particularly active against certain types of staphylococcus which produce penicillinase.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rabbit, cloxacillin was not teratogenic [1, 2]. Doses of 10–100 mg/kg throughout pregnancy had no harmful effects [1, 2]. High doses often resulted in maternal toxicity, and were lethal to the pregnant animals [1].

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Dicloxacillin sodium

(5-methyl-3-(2, 6-dichlorophenyl)-4-isoxazolyl-penicillin) sodium salt
(MW 510.3)

Not contra-indicated in pregnancy.

Dicloxacillin is a semi-synthetic penicillin which is resistant to acids and to penicillinase. It is therefore active orally, and effective against staphylococcus, which produce penicillinase.

Dicloxacillin crosses the placental barrier [7, 9]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, some authors suggest that the drug should be used with care in pregnancy because its safety has not been sufficiently proved clinically [1, 2]. In the literature consulted there was no evidence of embryofoetotoxic or teratogenic effects to lead us to conclude that dicloxacillin should be contra-indicated in pregnancy.

In the rabbit, dicloxacillin was neither embryofoetotoxic nor teratogenic [3, 4, 5, 6, 8]. Doses of 10–100 mg/kg throughout pregnancy were without harmful effects [5]. Doses of 50–100–200–500 mg/kg were not teratogenic, and only at the highest doses (50 times therapeutic) was there an increase in foetal resorptions compared to a control group [6].

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Flucloxacillin or sodium floxacillin

Floxapen, Magnapen,

6-(3-(2,6-chlorofluorophenyl)-5-methylisoxazole-4-carboxamido)-penicillanic acid sodium salt (MW 493.9)

Not contra-indicated in pregnancy.

Flucloxacillin is an orally active semi-synthetic penicillin which is penicillinase-resistant. It is used to treat staphylococcal infections and those which are resistant to other penicillins.

No reports have been found of embryofoetotoxic or teratogenic effects in the human foetus, or of adverse effects on the mother or the pregnancy.

No experimental studies have been described on the use of flucloxacillin in pregnancy in laboratory animals.

Metampicillin

D-(-)-6-(α -(methylene-amino)-phenylacetamido)-penicillamic acid (MW 361.25)

Not contra-indicated in pregnancy.

Metampicillin is a semi-synthetic penicillin with a wide spectrum of activity. Its molecular structure gives it high resistance to bacterial penicillinase. It has a very slight toxicity, and is particularly active against Gram-positive and Gram-negative bacteria.

Metampicillin crosses the placental barrier [1,4]. Administered intramuscularly at a dose of 1.5 g at the end of pregnancy, the drug is found 1 hour later in the amniotic fluid and foetal blood [1] at therapeutic concentrations [4]. Administration of metampicillin at various stages of pregnancy was neither embryofoetotoxic nor teratogenic [1,2,3]. Administered to 10 pregnant women at doses of 1.5–2 g both intramuscularly and orally, the drug had no harmful effects on the foetus or the mother [2].

No experimental studies have been described on the use of metampicillin in pregnancy in laboratory animals.

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Methicillin sodium

Celbenin, dimethoxyphenyl-penicillin sodium monohydrate (MW 420.4)

Not contra-indicated in pregnancy.

Methicillin is a semi-synthetic penicillin which is highly resistant to

penicillinase. It is active against all types of *Staphylococcus aureus*, particularly those which produce penicillinase (15–20 times more active). Methicillin is not as effective as penicillin G against other Gram-positive microorganisms, and is totally ineffective against Gram-negative bacteria, some of which can inactivate it.

Methicillin can cross the placental barrier [1,7]. After intravenous administration of 500 mg methicillin to pregnant patients, the drug was found in foetal serum after 15 minutes. Equilibrium between maternal and foetal concentrations was reached in 60 minutes. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [5, 6].

In the rabbit, methicillin was neither embryofoetotoxic nor teratogenic [2, 3]. Doses of 10–100 mg/kg (therapeutic dose = 4–6 g/day) were without harmful effects [3].

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Oxacillin sodium

5-methyl-3-phenyl-4-isoxazoly-1-penicillin sodium (MW 441.4)

Not contra-indicated in pregnancy.

Oxacillin is a semi-synthetic penicillin, active orally and resistant to penicillinase.

Oxacillin crosses the placental barrier [1], and is present in therapeutic levels in amniotic fluid [1]. The drug has been used in pregnancy without harmful effects on the foetus [1]. According to other authors, oxacillin should be used with care in pregnancy because its safety has not been sufficiently proved [2, 3]. However, no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and therefore we do not believe that oxacillin is contra-indicated in pregnancy.

Passage of oxacillin into breast milk is controversial. At most, it could be present only in very small quantities which could not harm the infant [1,4]. Some authors state that oxacillin administered to the nursing mother at doses of 500 mg/kg reaches bactericidal levels in the milk [1], but others maintain that the amount in milk is not measurable even after doses of 1 g/kg [4].

No experimental studies have been described on the use of oxacillin in pregnancy in laboratory animals.

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1.2 Tetracyclines

The tetracyclines are antibiotics with a wide spectrum of action, and they are able to penetrate into almost all tissues. They accumulate in the bones and in the reticuloendothelial system. They inhibit protein synthesis. There are numerous semi-synthetic compounds, each of which has its characteristic pharmacological and therapeutic actions. The following drugs are discussed in this section:

	Recommendation	Page
Chlortetracycline hydrochloride	C (P during lactation)	316
Tetracycline	C (P during lactation)	316
Oxytetracycline hydrochloride	C (P during lactation)	320
Demethylchlortetracycline	C (P during lactation)	321
Methacycline hydrochloride	C (P during lactation)	322
Lymecycline	C (P during lactation)	323
Doxicycline hydrochloride	C	323
Guamecycline	C (P during lactation)	324
Minocycline	C (P during lactation)	325
Pipacycline	C (P during lactation)	326
Aminochlortenoxycline	C (P during lactation)	326
Clomocycline	C (P during lactation)	327
Rolitetracycline	C (P during lactation)	327

During pregnancy, particularly after the fourth month, all the tetracyclines are contra-indicated because of their negative effects on bone and dental development. Teratogenic effects are doubtful after administration during the embryonic period. Perhaps these are related to lack of folates when they occur.

Intravenous therapy with very high doses of tetracyclines (above 2.5 g/day) can cause hepatic steatosis in the pregnant woman as well as pancreatitis and renal insufficiency. Pregnancy increased the inhibitory effects of the tetracyclines on protein synthesis.

Chlortetracycline hydrochloride

Aureomycin, Aureocort, Deteclo, Propaderm A, Trimovate,
 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide (MW 515.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy, and should be used with care during lactation.

Chlortetracycline is a natural antibiotic, produced by *Streptomyces aureofaciens*, from which almost all the semi-synthetic analogues have been derived. It has a wide spectrum of antimicrobial activity (Gram-positive, Gram-negative) which also includes the mycobacteria, the rickettsias, and the amoebae. The mechanism of action of chlortetracycline is analogous to that of the aminoglycoside antibiotics: it forms bonds with ribosomes which results in inhibition of protein synthesis.

Chlortetracycline is partially absorbed when taken orally, and binds to plasma proteins. It is excreted mainly through the bile, with enterohepatic recirculation. It crosses the blood-brain barrier to some extent, but penetrates extremely well into all other biological fluids and tissues, while it accumulates in the reticuloendothelial system, in the bones, and in the teeth. Chlortetracycline is mainly eliminated in the faeces and to a lesser degree in the urine. It can produce hepatotoxicity, particularly during pregnancy [5, 6].

The tetracyclines also have an inhibitory action on protein metabolism, which is proportional to the dose administered, to renal function, the duration of therapy, and to modifications induced by the drug on intestinal flora. They increase urinary elimination of vitamin B₁₂ and of folic acid. The tetracyclines can chelate with calcium, forming complexes in the teeth and in the bones which initially have a yellow fluorescence which later turns brown. It is then non-fluorescent and permanent, and consists of oxidation products of the antibiotic [10].

Chlortetracycline crosses the placental barrier, and reaches foetal blood in a concentration equal to 1/14th that of maternal levels. It is also found in the amniotic fluid. Passage into breast milk limits its use during lactation [1, 8, 9, 11, 12, 13]. Chlortetracycline has similar effects to tetracycline (page 316) in both the pregnant women and the foetus.

In the rat and mouse, chlortetracycline caused embryofoetotoxic effects (retardation of skeletal development), but was not teratogenic [1, 2, 3]. Other authors did not observe embryofoetotoxic effects in the rat. A dose of 11% in the diet throughout pregnancy was without harmful effects [7]. In the mouse, subcutaneous administration of 125 mg/kg from the 10th to the 18th day of pregnancy was not teratogenic, although there was a retardation in growth and an increase in foetal resorption [2]. Administration of 62–125 mg/kg subcutaneously from the 1st to the 7th day of pregnancy caused only an increase in foetal reception [3].

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Tetracycline

Achromycin, Tetrachel, Sustamycin, Tetrex, Chymocylar, Albamycin T, (MW 444.43)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy and should be used with care during lactation.

Tetracycline is a semi-synthetic antibiotic which is obtained from the natural product, chlortetracycline. It has many similarities to the latter, particularly with regard to its antibacterial spectrum, its mechanism of action, and its distribution in various tissues (see chlortetracycline, page 316). Tetracycline is partially absorbed from the digestive tract, has a slight affinity for plasma proteins, and is eliminated to a large extent in the urine.

Tetracycline crosses the placental barrier [6, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36, 42, 44]. In addition to an increased urinary elimination of riboflavin and of folates in the mother, an increase in hepatic parenchyma toxicity (tetracycline-induced fatty liver of pregnancy [37]) has been reported. During therapy for pyelonephritis in pregnancy, in six cases the appearance of hepatic steatosis, hypocholesterolaemia, hypopotassemia, hyponatraemia, nausea, vomiting, diarrhoea, and gastrointestinal haemorrhage have been observed [37].

In the foetus, tetracycline chelates with calcium and is deposited in the bones and in the dental enamel. Administration of the antibiotic in the last part of pregnancy can cause a reduction in foetal bone development and a brown coloration of the teeth when they appear, as well as hypoplasia of the enamel [5, 6, 7, 8, 9, 29, 35, 41, 42, 43, 45, 46]. This is particularly noticeable when the

antibiotic is administered after the fourth month of pregnancy [10,40]. In a retrospective study a correlation was demonstrated between therapy and dental hypoplasia [11]. Tetracycline therapy during the early stages of pregnancy (the embryonic period) can cause teratogenic effects. There are sporadic references to this in the literature. Cases have been reported of malformation of the hands [1], and of cataracts [2]. A retrospective study on 133 pregnant women treated over a long period for urinary infections did not show any malformations [4].

Tetracycline passes into breast milk, and 20 hours after administration reaches a concentration of 20–90% of that in maternal serum [12,38].

In the mouse, rat, rabbit, and chick embryo, tetracycline was not teratogenic [22,23] but it was embryofetotoxic at higher doses, causing retardation of skeletal development [16,17,18,19,20,21,30]. Cases of teratogenicity in the rat and mouse have, however, been recorded [15,39]. In the rat, oral doses of 5 mg/day from the 5th to the 20th day of pregnancy caused cleft palate [15]. Oral doses of 40 mg/kg from the 10th to the 15th day of pregnancy were embryofetotoxic [16]. Oral doses of 150–200 mg/kg from the 1st to the 18th day of pregnancy were fetotoxic [17]. Intraperitoneal doses of 85 mg/kg from the 14th to the 18th day of pregnancy were embryofetotoxic [18]. Doses of 50–85 mg/kg from the 7th to the 15th day of pregnancy were embryofetotoxic [19].

In the mouse, subcutaneous doses of 250 mg/kg from the 10th to the 18th day of pregnancy were embryofetotoxic [20]. Doses of 125–250 mg/kg subcutaneously from the 1st to the 7th day of pregnancy were embryotoxic [21]. Doses of 100 mg/kg orally from the 6th to the 15th day of pregnancy were not teratogenic [22]. A dose of 5 mg/day from the 5th to the 20th day of pregnancy produced cleft palate with hypoplasia of the mandibula in 30% of embryos, with malformations of the limbs, including syndactyly and shortening, in 33% [39].

In the rabbit, doses of 100 mg/kg orally from the 6th to the 18th day of pregnancy were not teratogenic [22]. Intraperitoneal or intravenous doses of 30–230 mg/kg on the 9th day of pregnancy were not teratogenic [23]. In chick embryo, administration of 2–5 μ g tetracycline caused retardation of bone development [30].

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Oxytetracycline hydrochloride

Terramycin, Abbocin, Berkmycen, Galenomycin, Oxymycin (MW 496.9)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy and should be used with care during lactation.

Oxytetracycline is a natural antibiotic produced by *Streptomyces rimosus*. Its pharmacological characteristics are almost identical to those of chlortetracycline (see page 316).

Oxytetracycline crosses the placental barrier [6,7,8] and is found in the foetus in concentrations equal to 1/4th those of maternal plasma [6]. The drug is contra-indicated in pregnancy because of its adverse effects on the development of teeth and bones (see tetracycline, page 318).

Oxytetracycline passes into breast milk [9], and therefore administration during the puerperium should be carefully controlled and monitored.

In the rat, mouse, chick embryo, and rabbit, oxytetracycline has variable effects, depending on the species and the dose. In some cases it had an embryo-foetotoxic but not a teratogenic effect [1,5], while in the rabbit and chick embryo it could be both embryofoetotoxic and teratogenic [2,3].

In the rat, intramuscular doses of 41.5 mg/kg from the 7th to the 18th day of pregnancy were neither embryofoetotoxic nor teratogenic [3]. In the mouse, subcutaneous doses of 100 mg/kg from the 10th to the 18th day of pregnancy were embryofoetotoxic but not teratogenic [5]. In the rabbit, intramuscular doses of 41.5 mg/kg from the 10th to the 28th day of pregnancy were embryofoetotoxic and teratogenic [3].

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Demethylchlortetracycline or demeclocycline

Deteclo, Ledermix, Ledermycin,

7-chloro-6-demethyltetracycline (MW 464.88)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy and should be used with care during lactation.

Demeclocycline is isolated from a mutant strain of *Streptomyces aureofaciens*, and possesses an antibacterial spectrum and mechanism of action similar to those of other tetracyclines. It differs in having a longer plasma half life which allows lower doses to be administered, binds to plasma proteins, and has a low renal clearance.

Demeclocycline crosses the placental barrier [1, 5]. It is contra-indicated in pregnancy because of its effects on dentition [2, 5, 6, 7, 8, 9]. For further details, see tetracycline (page 318; inhibition of protein synthesis increase in folate elimination, reduction in bone growth, etc.).

In the mouse, demeclocycline was embryofoetotoxic and teratogenic [4, 5]. Oral doses of 300–600 mg/kg from the 8th to the 13th day of pregnancy caused cleft palate [4].

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Methacycline hydrochloride

Randomycin,

6-methylene-5-hydroxytetracycline hydrochloride (MW 478.9)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy and should be used with care in lactation.

Methacycline is a tetracycline which can be distinguished by its greater therapeutic activity at equivalent doses. It binds strongly to plasma proteins, and has a reduced renal clearance. Its mechanism of action is based upon inhibition of bacterial protein synthesis in the ribosomes.

Methacycline crosses the placental barrier, but to a lesser extent than other tetracyclines [1, 4, 5]. Some authors believe that the drug is harmless in pregnancy, and does not have teratogenic effects at any stage [2]. Oral administration of methacycline to 23 patients at various stages of pregnancy at doses of 600 mg/day for periods varying from 3–8 days did not produce embryofoetotoxic or teratogenic effects [2]. However, we believe that methacycline should not be administered in the last two trimesters, because of possible effects on bone growth and dentition. For further details, see tetracycline (page 318).

In the rat, methacycline crosses the placental barrier [3]. Oral doses of 50 mg/kg or intravenous doses of 20 mg/kg produced maximal blood levels in the foetus after 12 hours [3].

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Lymecycline

Tetralsal, tetracycline-L-methylenelysine (MW 602.63)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy, and should be used with care during lactation.

Lymecycline is a tetracycline derivative which possesses a wide spectrum of activity, low toxicity, and rapid excretion in the bile and urine.

Lymecycline passes into amniotic fluid and cord blood [1]. Other studies, although confirming transplacental passage of the drug, have not found it in amniotic fluid [2,4]. Administration of lymecycline to pregnant patients with sudden membrane rupture did not cause toxic effects in either the mother or the foetus [1]. Prolonged use during pregnancy could cause inhibition of protein anabolism, as occurs with other tetracyclines (see tetracycline, page 318), and lymecycline also forms fluorescent chelates which subsequently turn brown in teeth and bone.

In the chick embryo, lymecycline was neither embryofetotoxic nor teratogenic. At doses of ten times therapeutic, however, it affected bone growth [3]. A dose of 2.5 µg/g injected into the yolk on the 4th day of incubation was without harmful effects, but a dose of 25 µg/g caused foetal death, inhibition of bone growth, and sporadic limb malformations [3].

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Doxycycline hydrochloride

Vibramycin, α-6-desoxy-5-hydroxytetracycline (MW 512.9)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Doxycycline is a semi-synthetic derivative of oxytetracycline which differs from other tetracyclines by virtue of its higher blood concentrations resulting from its rapid gastrointestinal absorption, higher tissue concentrations, and slow urinary excretion. Elimination occurs almost completely in the faeces, but in an inactive form which does not destroy intestinal flora. Such properties produce an antibacterial potency which is superior to and more prolonged than that of other tetracyclines.

Doxycycline crosses the placental barrier [1] and reaches foetal blood concentrations of 40–60% those of maternal plasma [7]. No evidence is forthcoming on teratogenic effects of doxycycline, and there are many references to normal infants born to women treated with this drug in pregnancy [2]. However, doxycycline does have effects on protein metabolism, folic acid metabolism, and cyanocobalamin, as well as on bone and teeth (see tetracycline, page 318), and therefore we believe that its use is contra-indicated in pregnancy.

Elimination of doxycycline in milk is small, and is not important enough to affect the infant [1].

In the mouse, rabbit, rat, and monkey, doxycycline was not teratogenic [4, 6], and harmful effects appeared only at doses 25 times greater than therapeutic [3]. In the rat, transplacental passage of the drug has been demonstrated 30 minutes after intravenous administration of 20 $\mu\text{g}/\text{kg}$ or after oral administration of 50 $\mu\text{g}/\text{kg}$ [5]. In the mouse, oral doses of 66.6 mg/kg from the 3rd to the 15th day of pregnancy did not significantly affect the pregnancy and were not teratogenic. Birth and development of animals at term was unaffected [6]. Similar does in the rat were likewise without harmful effects [4].

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Guamecycline

N', N'-diethyleniminobiguanido-methyltetracycline dihydrochloride
(MW 626.68)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy, and should be used with care during lactation.

Guamecycline is a synthetic tetracycline derivative which possesses the same antibacterial spectrum as tetracycline, equivalent toxicity, is well tolerated locally and systemically, and has high therapeutic efficacy (with doses lower than those usually employed with the tetracyclines). It has a particular affinity for the bronchopulmonary tract.

Guamecycline crosses the placental barrier at therapeutic doses, a maximum concentration being reached 7–8 hours after administration [1]. It is present in the amniotic fluid 3 hours after administration [1]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, as guamecycline is a tetracycline, its effects on bone and teeth should be considered (see tetracycline, page 318), and it is therefore contra-indicated in pregnancy.

Guamecycline passes into breast milk in low doses [2], but more rapidly than do other tetracyclines [3]. It should be administered with caution during lactation, because of possible effects on bone and teeth [4].

No experimental studies have been described on the use of guamecycline in pregnancy in laboratory animals.

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Minocycline

Minocin, 7-dimethylamino-6-deoxy-6-demethyltetracycline (MW 457.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy, and should be used with care during lactation.

Minocycline is a semi-synthetic tetracycline with a wide antibacterial spectrum. It is active against staphylococci, even resistant strains. Minocycline is rapidly metabolized, and very little is eliminated in the active form. It also accumulates in the tissues. Its characteristic liposolubility facilitates its penetration into body fluids, the brain, and fat deposits.

The effects of administration of minocycline in pregnancy are similar to those of other tetracyclines (see tetracycline, page 318). We believe that it is contra-indicated in pregnancy because of its effects on teeth and bone. Minocycline crosses the placental barrier [2, 4] and passes into breast milk [2, 4].

In the rat and rabbit, minocycline was foetotoxic, but it was not teratogenic in the rabbit [1]. In the rat, oral doses of 50–100 mg/kg for three reproductive cycles did not affect development, fertility, reproduction, or lactation, and there were no embryofoetotoxic effects [1]. In the rabbit, oral doses of 25–75 mg/kg for three reproductive cycles provoked a significant diminution in weight gain in the neonates, from the 15th to the 30th day following birth [1].

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Pipacycline

4- β -hydroxyethyl-diethylene-diaminomethyl-tetracycline (MW 586.63)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy, and should be used with care during lactation.

Pipacycline is derived from mepicycline, and is used particularly in infections of the respiratory tract.

Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, pipacycline is contra-indicated in pregnancy because of potential effects on bone and teeth (see tetracycline, page 318). The manufacturers concur with this view [1].

No experimental studies have been described on the use of pipacycline in pregnancy in laboratory animals.

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Aminochlortenoxycline

double sulphate of tetracycline (MW 444.43) and of 2-(β -chloroethyl)-2,3,-dihydro-4-oxo-6-aminobenzo-1,3-oxazine (MW 226.68)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

Contra-indicated in pregnancy, and should be used with care during lactation.

Aminochlortenoxycycline is a salt of tetracycline, useful in respiratory infections.

Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, aminochlortenoxycycline is contra-indicated in pregnancy because of its potential effects on bone and teeth (see tetracycline, page 318).

In the rat, aminochlortenoxycycline was neither embryofetotoxic nor teratogenic [1]. Oral doses of 100 mg/kg throughout pregnancy did not increase the incidence of mortality in mothers or foetuses. There were no skeletal anomalies in the neonates at birth [1].

Bibliography

[1] Comunicazione personale della Ditta Ici - Milano.

Clomocycline

Megaclor, *N*-methylol-chlortetracycline (MW 508.93)

Rolitetracycline

pyrrolidine-methyltetracycline (MW 527.56)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		P

The effects of administration of these two drugs in pregnancy are similar to those of other tetracyclines (see tetracycline, page 318), and therefore we believe that they are contra-indicated in pregnancy and should be used with care during lactation, because of their potential effects on bone and teeth.

1.3 Aminoglycosides

The aminoglycoside antibiotics are characterized by their serious toxicity in the ear and kidney. They are only slightly absorbed orally and cause inhibition of protein synthesis. The following antibiotics are discussed here:

	Recommendation	Page
Dihydrostreptomycin	P	328
Streptomycin sulphate	P	328
Gentamicin	P	331
Tobramycin	P	333
Sisomycin sulphate	P	333
Kanamycin sulphate	P	334
Bekanamycin sulphate	P	336
Paramomycin	NC (orally)	337
Neomycin sulphate	NC (orally)	337

Because of their foetotoxicity, the aminoglycoside antibiotics should be used with care during pregnancy, particularly when administered systemically. Low doses over short periods should be used. These limitations do not, however, apply to the aminoglycoside antibiotics when they are administered orally, because they are only slightly absorbed.

Dihydrostreptomycin

Guanimycin (MW 1461.4)

Streptomycin sulphate

Streptomycin Glaxo, Streptotriad, Cremostrep (MW 1457.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		P

To be used with care in pregnancy and during lactation.

Streptomycin is an antibiotic with an aminoglycoside structure. Its fundamental pharmacological characteristics are: slight oral absorption, bacteriostatic and bactericidal action only on Gram-negative organisms, ototoxicity and nephrotoxicity, mechanism of action based on inhibition of protein synthesis in the ribosomes.

Streptomycin crosses the placental barrier [1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 44, 56, 57, 61, 64]. Administered at the end of pregnancy by the intramuscular and intravenous routes, it is found in foetal blood in quantities varying between $\frac{1}{3}$ and $\frac{1}{2}$ the maternal blood concentration [6, 7, 8, 9, 10, 13]. In premature infants, streptomycin is found in tuberculostatic concentrations both in blood and spinal fluid [12]. It is sometimes present in low amounts in amniotic fluid [6, 7, 8], according to some authors, while other studies have suggested that its concentration is consistently higher than that in foetal blood.

At all stages of pregnancy, streptomycin can cause damage to the internal ear (cochlear-vestibular structures) of the foetus, with consequent hearing defects after birth [4, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 28, 29, 30, 55, 58, 64, 65], as well as damage to the eighth cranial nerve [21, 28, 29, 30, 55, 59, 60]. It is not, however, teratogenic [17, 27]. Some authors claim to have observed micromelia and various skeletal anomalies in infants born to patients treated with streptomycin [13, 28, 29, 30]. Some [54] maintain that the drug is definitely teratogenic when administered in the first trimester. Others [31, 34, 45, 46, 47, 48, 49, 50, 51, 52, 53], however, exclude any type of foetal damage with doses of up to 1 g/day. One study stated that there could be embryofoetotoxic effects at therapeutic doses only in the event of changes in maternal renal

function [4]. Maternal levels of streptomycin remain higher than foetal levels, even after prolonged therapy [12, 13, 32, 33, 35]. The concentration of the drug in amniotic fluid is generally higher than in foetal blood [9].

Streptomycin passes into breast milk, albeit in small quantities [36], and should therefore be used with care during lactation [62, 63].

In the rat, mouse, and guinea-pig, streptomycin was embryofoetotoxic and teratogenic [18, 36, 38, 39, 40, 41, 42, 43]. In the rat, a dose of 100–500 mg/kg in one or more intramuscular injections from the 5th day to the end of pregnancy caused an increase in embryonal mortality, malformations, and diminution in hearing [36]. Intraperitoneal doses of 10–150 mg/kg throughout pregnancy were teratogenic and caused hearing defects [18, 38]. Doses of 1.25–125 mg/kg in one or more oral doses from the 6th to the 14th day of pregnancy were neither embryofoetotoxic nor teratogenic [39]. Oral doses of 10 mg/kg throughout pregnancy caused an increase in mortality in the embryo but no malformations [40].

In the mouse, intramuscular doses of 500 mg/kg from the 9th to the 13th day of pregnancy did not affect embryonal mortality, nor did they produce macroscopic malformations or affect the central nervous system, except that in some cases microscopic cerebral changes were observed. These were, however, difficult to evaluate [41].

In the guinea-pig, subcutaneous doses of 25–300 mg/kg throughout pregnancy caused an increase in the mortality of the embryo and defects of hearing [42]. Intramuscular doses of 25–30 mg/kg from the 5th to the 6th week before termination of pregnancy were embryotoxic but not teratogenic, producing placental damage such as hyperaemia, haemorrhage, and endometrial necrobiosis [43].

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Gentamicin

Gentacin, Garamycin, Cidomycin, Gentisone (MW 477.59)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Gentamicin is an aminoglycoside antibiotic, produced by two different species of *Micromonospora*. Its mechanism of action is analogous to that of streptomycin, that is, it inhibits protein synthesis in the ribosomes and alters transmission of the genetic code. Since its gastrointestinal absorption is poor, gentamicin is administered parenterally. It binds to plasma proteins and is excreted in the urine, where it reaches very high concentrations. Its most important side effects are ototoxicity and nephrotoxicity. Gentamicin is used in the therapy of many infections, as it has a wide spectrum of activity. Its efficacy in the treatment of urinary infection is greater when the urine is alkaline [22, 23, 24, 25, 26, 27].

Gentamicin crosses the placental barrier [1, 2, 3, 9, 12, 13, 14, 15, 16, 17, 18, 21, 29, 31]. Administered at an initial dose of 45 mg and then by infusion at a dose of 20 mg/hour, it reaches a concentration of 1–2 $\mu\text{g/ml}$ in foetal blood after a few hours, which is only slightly less than maternal blood levels [3]. After intramuscular administration of gentamicin in a single dose of 80 mg during labour, the drug is found in cord blood in amounts which never exceed 0.5 $\mu\text{g/ml}$. Gentamicin is also found in amniotic fluid, but the concentration reached is not sufficient for antibacterial action [18]. Administered to pregnant women at a dose of 80 mg, followed by infusion of 18.5 mg/hour, gentamicin reaches mean serum concentrations which vary between 2.1 and 6.2 $\mu\text{g/ml}$, and is detectable in foetal venous blood and cord blood [28].

Gentamicin should be used with care in pregnancy because of its possible toxic effects on the eighth cranial nerves, with maternal and foetal deafness [4, 5, 6, 7, 8, 11, 12, 17, 32, 33]. However, gentamicin at therapeutic levels in maternal serum produces foetal serum concentrations which are well below those which cause damage to the eighth cranial nerves in the already developed foetus [28]. Gentamicin administered for urinary infections in 50 pregnant

women at doses of 2 mg/kg/day for 5 days had no harmful effects on the foetus [30].

Gentamicin passes into breast milk in moderate amounts [13]. After administration of 80 mg to the mother, concentrations of gentamicin in milk were $\frac{1}{3}$ those in maternal plasma; they were not measurable in the neonate [13].

In the rat and rabbit, gentamicin did not affect embryonic development, evolution of the pregnancy, or lactation [19, 20].

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Tobramicin

Nebcin,

O-(3-amino-3-deoxy- α -D-glucopyranosyl-(1,4))-*O*-(2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexapyranosyl-(1,6))-2-deoxystreptamine (MW 467.54)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Tobramicin has an aminoglycoside structure similar to that of gentamicin (see page 331). It is used principally in infections caused by *staphylococcus*, *escherichia*, and *pseudomonas*. when the pathogenic organism is resistant to gentamicin.

Tobramicin crosses the placental barrier [1]. Administered intramuscularly at a dose of 2 mg/kg to 33 patients before therapeutic abortion, tobramycin was found in foetal blood at a concentration equal to 20% of that in the mother [1]. Administration of tobramycin in pregnancy requires care, because its safety has not been sufficiently proved [4], and the manufacturers concur with this view [2].

In the rat and rabbit, tobramycin was not teratogenic [3]. In the rat, subcutaneous doses of 100 mg/kg/day during the period of organogenesis and early foetal development were without harmful effects [3]. In the rabbit, doses of 20–40 mg/kg/day at various stages of pregnancy were harmless. Renal damage in the pregnant animal has been described, but only at very high doses [3].

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Sisomicin sulphate or sissomicin sulphate

*O*⁴-(2,6-diamino-2,3,4,6-tetradesoxy- α -D-glycero-hex-4-enopyranosyl)-*O*⁶-(3-desoxy-4-C-methyl-3-methylamino- β -L-arabinopyranosyl)-2-deoxystreptamine sulphate

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Sisomicin is an aminoglycoside antibiotic with properties similar to those of gentamicin and tobramycin. It is isolated from a culture of *Micronospora inydensis*, an actinomycete found in California in the Inyo forest. Its spectrum of activity means that it can be used against *Staphylococcus* species, including penicillin and methicillin resistant strains, *Pseudomonas aeruginosa*, *Escherichia coli*, species of *Klebsiella*, *Enterobacter-serratia-proteus* (indole positive and negative), and *Citrobacter*. The plasma half life of sisomicin is about 2 hours, with a therapeutic activity which lasts for 6–8 hours and is based upon inhibition of protein synthesis in the bacterial cell. Sisomicin is ototoxic and nephrotoxic, as are other aminoglycosides (see gentamicin and tobramycin, pages 331 and 333).

Sisomicin crosses the placental barrier [4]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, sisomicin should be used with care in pregnancy because of its structure [3].

In the rat and rabbit, sisomicin was not teratogenic [1] and did not affect reproduction in the rat [2].

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Kanamycin sulphate

Kannasyn, Kantrex,

4, 6-diamino-2-hydroxy-1, 3-cyclohexene-3, 6'-diamino-3, 6'-didesoxy-di- α -glucoside sulphate (MW 582.6)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		P

To be used with care in pregnancy and during lactation.

Kanamycin is a bacteriostatic and bactericidal antibiotic with a wide spectrum of activity, which extends from Gram-positive to Gram-negative and tubercular mycobacteriae. It is almost inactive orally and thus is administered only by the parenteral route, it does not bind to plasma proteins, and it is eliminated in the urine, mainly by glomerular filtration. If renal function is impaired, as in neonates, accumulation may occur. Kanamycin is ototoxic and nephrotoxic, therefore therapy requires careful control and limitation of dosage. Its mechanism of action is similar to that of streptomycin (page 328).

Kanamycin crosses the placental barrier [1, 19, 21, 23]. It is present to only a small extent in amniotic fluid [2]. Kanamycin should be used with care in pregnancy because although it is not teratogenic, it may cause deafness in the foetus [4, 5, 6, 7, 8, 9, 10, 12, 19, 20, 22, 24, 25, 26, 28]. In 391 patients who had taken the drug during pregnancy at a dose of 50 mg/kg, 9 infants had hearing defects [10]. One case of intra-uterine ototoxicity was reported. The mother had taken 4.5 g kanamycin together with ethacrynic acid in the 28th week of pregnancy [12]. In another study, the tissues of 5 embryos were examined following administration of kanamycin to the mothers for 3 days prior to abortion at a dose of 1 g/day from the 6th to the 8th week of pregnancy. No abnormalities were found [13]. Other authors maintain that kanamycin can damage the foetus only when administered in very high doses to the mother, or when there is diminished maternal renal function [1].

Kanamycin passes into breast milk, and may cause toxic effects in the nursing infant [27].

In the rat, and guinea-pig, kanamycin was embryofetotoxic and teratogenic [14, 16, 17, 18]. In the rat, intramuscular doses of 200 mg/kg throughout pregnancy were teratogenic [14]. A dose of 100 mg/kg from the 8th to the 16th day of pregnancy was without harmful effects [15]. A dose of 200 mg/kg from the 5th to the 20th day of pregnancy caused malformations of the urogenital system [16]. Subcutaneous doses of 300–400 mg/kg from the 1st to the 12th day or from the 12th to the 20th day of pregnancy were embryofetotoxic and teratogenic [17].

In the guinea-pig, a dose of 200 mg/kg was embryofetotoxic and teratogenic [18].

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Bekanamycin sulphate or kanamycin B sulphate or Kanendomycin

O⁴-(3-amino-3-desoxy- α -D-flucopyranosyl)-O⁶-(2, 6-diamino-2, 6-didesoxy- α -D-leucopyranosyl)-2-desoxystreptamine sulphate (MW 483.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Kanamycin B is an aminoglycoside antibiotic produced by a mutant strain of *Streptomyces kanamyceticus*. It is administered intramuscularly, and reaches maximum concentrations within 1 hour. It is mainly distributed in the kidneys, lungs, spleen, heart, liver, and gall bladder, and is eliminated in the urine. The toxicity of kanamycin B is slightly less than that of kanamycin and affects both the kidneys and the cochlear-vestibular organs, as do other aminoglycosides. Kanamycin B is active against Gram-positive and Gram-negative organisms and against mycobacteria, and is used in infections of the respiratory tract, the biliary and urinary tracts, and in sepsis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, we believe that kanamycin B should be used with care in pregnancy because of its potential toxic effects (see kanamycin, page 334).

In laboratory animals (mouse, rat) at doses of 5, 10, and 20 times the therapeutic dose in man, kanamycin is neither embryofoetotoxic nor teratogenic [1].

In the rat, kanamycin administered intramuscularly at therapeutic doses, from the 9th to the 14th day of pregnancy, produced no associated effects on the foetus [2].

In the mouse and rat, a dose of 50–100–200 mg/kg given intramuscularly from the 7th to the 12th day of pregnancy was not embryofoetotoxic or teratogenic [2].

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Paramomycin or aminosidin sulphate

(MW 615.65)

Not contra-indicated in pregnancy.

Paramomycin is an aminoglycoside antibiotic which like other such drugs (streptomycin, kanamycin, gentamicin) is only slightly absorbed orally. It has bacteriostatic and bacteriocidal activity on Gram-negative organisms, and acts by inhibition of protein synthesis (see streptomycin, page 328). Paramomycin is administered only orally, and is also an amoebicide and a tenicide.

Because of its minimal absorption, there have been no reports of harmful effects on the foetus, the mother, or the pregnancy [1, 2, 3].

In most species of laboratory animals, paramomycin was not teratogenic [4]. In chick embryo, it produced malformations when administered at high doses [5, 6]. When injected into chick embryos on the 3rd day of incubation at a dose of 2 mg, it had no harmful effects. When the dose was increased to 5–10–15 mg, there were deformities of the beak, hypoplasia of the upper and lower jaws, aplasia of the cranium, etc. [5, 6].

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Neomycin sulphate

Audicort, Betnesol, Granodin, etc. (MW 626.7)

Not contra-indicated in pregnancy.

Neomycin is an antibiotic produced by *Streptomyces fradiae*, and it has a wide spectrum of activity and a similar mechanism of action to that of streptomycin (see page 328). It is used topically, orally (although its absorption is slight), and intramuscularly. Unfortunately, it is very toxic, particularly in the kidneys and acoustic nerve, as is streptomycin. It also affects intestinal absorption of certain foodstuffs. Neomycin is therefore mainly used in dermatological preparations, and in preparation for intestinal surgery and hepatic coma. In other fields, more manageable antibiotics are now used.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, as would be expected considering the minimal oral absorption of neomycin. However, parenteral administration is to be avoided because of potential ototoxicity [1, 2, 4].

Neomycin passes into breast milk [3].

No experimental studies have been described on the use of neomycin in pregnancy in laboratory animals.

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1.4 Macrolides

The macrolide antibiotics, so called because of the presence of a lactone ring associated with various desoxy sugars, are particularly active in inhibiting protein synthesis in Gram-positive bacteria. The following drugs are discussed in this section:

	Recommendation	Page
Erythromycin	NC	338
Oleandomycin phosphate	NC	339
Troleandomycin	NC	340
Spiramycin	NC	340
Kitasamycin	NC	341

The macrolide antibiotics are not contra-indicated during pregnancy, even although there is little information concerning some of them in the literature.

Erythromycin

Erythroped, Erythrocin, Ilatcin, Ceplac, Erythromid, Ilosone (MW 733.0)

Not contra-indicated in pregnancy.

Erythromycin is a macrolide antibiotic and has bacteriostatic and bacteriocidal actions, particularly on Gram-positive organisms. It acts on ribosomes inhibiting protein synthesis and in particular the formation of long-chain peptides. Erythromycin is active orally (depending on the degree of salt formation) and parenterally. It readily dissolves in tissues and in biological fluids, including bile. In the form of an estolate, erythromycin can cause intrahepatic cholestasis and should be avoided in patients with liver problems.

Erythromycin crosses the placental barrier [1,2,3,4,14,17] and reaches foetal blood concentrations of 5–20% of those in maternal blood [1]. In 14 patients transplacental passage of the drug was observed in the 12th to 14th week of pregnancy, with doses of 500 mg [6]. No reports have been found of harmful effects on the foetus, the mother, or the pregnancy [12,13,15,17,18,19].

Erythromycin passes into breast milk, reaching a concentration which is greater than that in plasma [8,16].

In the rat, erythromycin was embryofetotoxic and teratogenic [11]. Subcutaneous doses of 10–25 mg/kg from the 6th to the 10th day of pregnancy were damaging to the foetus [11].

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Oleandomycin phosphate

(MW 785.9)

Not contra-indicated in pregnancy.

Oleandomycin is a macrolide antibiotic produced by *Streptomyces antibioticus*. Among its semisynthetic derivatives, the most active is triacetyl-oleandomycin. Oleandomycin is both bacteriostatic and bacteriocidal, with a wide spectrum of activity. Its mechanism of action is unknown, but is probably similar to that of erythromycin, affecting bacterial protein synthesis.

Oleandomycin has been used in late pregnancy without hepatotoxicity in the mother [1], and no harmful effects have been reported in the infant.

Oleandomycin passes into breast milk in quantities sufficient to cause inhibition in cultures of *Micrococcus pyogenes*, *Aureus*, and *Subtilis* [2,3].

No experimental studies have been described on the use of oleandomycin in pregnancy in laboratory animals.

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Troleandomycin

triacetyloleandomycin (MW 813.96)

Not contra-indicated in pregnancy.

Troleandomycin is a semi-synthetic derivative of oleandomycin.

Troleandomycin crosses the placental barrier. Administered to 25 mothers in a single dose of 250 mg, the drug was found in cord blood 12 hours later in three cases [1]. No harmful effects have been observed in the foetus, the mother, or the pregnancy [2, 3]. However, some authors [4, 5] advise against its use in pregnancy.

No experimental studies have been described on the use of troleandomycin in pregnancy in laboratory animals.

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Spiramycin

(MW 843.04)

Not contra-indicated in pregnancy.

Spiramycin is a macrolide antibiotic which is particularly active against Gram-positive bacteria. Its mechanism of action is based on inhibition of protein synthesis, and it has been used successfully in the treatment of toxoplasmosis.

Spiramycin crosses the placental barrier [1, 8], but according to some authors this effect is inconsistent and occurs at very variable concentrations [2, 3]. Administered to 12 mothers at a dose of 2 g/day, spiramycin appeared in cord blood at a concentration of 0.5 $\mu\text{g/ml}$ [1]. Administered to 14 mothers at a dose of 3 g/day, the drug was found at levels of 0.7 $\mu\text{g/ml}$ in cord blood [1]. Spiramycin has been used at various stages of pregnancy as an antiprotozoic, and had no embryofoetotoxic or teratogenic effects [8, 9, 10, 11, 12, 13, 14, 15, 16].

Passage of spiramycin into breast milk has been demonstrated [6]. Administration of the drug at doses of 1.5 g for 3 days to nursing mothers

produced concentrations of 20 $\mu\text{g/ml}$ in the infant, at which level it exerted a bacteriostatic effect [6].

In laboratory animals, spiramycin was neither embryofetotoxic nor teratogenic [4].

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Kitasamycin

(MW 785.94)

Not contra-indicated in pregnancy.

Kitasamycin is a wide-spectrum antibiotic with a macrolide structure, and is isolated from cultures of *Streptomyces kitasato eusis*.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In laboratory animals, kitasamycin was neither embryofetotoxic nor teratogenic [1].

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1.5 Cephalosporin

The cephalosporins are semi-synthetic antibiotics with a wide antibacterial spectrum. They contain a β -lactam ring degradable by penicillinase (β -lactamase). Numerous derivatives with analogous therapeutic activity can be obtained by substitution in the 7-aminocephalosporanic acid nucleus, but these have different pharmacodynamic properties.

The mechanism of action of the cephalosporins is similar to that of penicillin, and is by inhibition of protein synthesis in the bacterial cell walls. The derivative cephaloridine is nephrotoxic. The following drugs are discussed in this section:

	Recommendation	Page
Cephalothin sodium	NC	342
Cephazolin	NC	343
Cephaloridine	NC	344
Cephalexin	NC	345
Cephradine	NC	346
Cephacetrile	NC	347
Cefuroxime sodium	NC	347
Cefoxitin sodium	NC	348

The cephalosporins cross the placental barrier and reach therapeutic levels in the foetus. They are not contra-indicated at any stage of pregnancy, because embryofoetotoxic or teratogenic effects have never been observed, either in man or laboratory animals.

Cephalothin sodium

Keflin, sodium salt of

7-(thiophene-2-acetamido)-cephalosporanic acid (MW 418.4)

Not contra-indicated in pregnancy.

Cephalothin is a semi-synthetic antibiotic derived from cephalosporin C, and is effective against numerous Gram-positive and Gram-negative bacteria, in which it inhibits cell wall synthesis. Cephalothin is only slightly absorbed from the digestive tract, and is therefore used parenterally. It crosses the blood-brain barrier only in minimal amounts, binds to plasma proteins, and is secreted in its active form in the renal tubules. This elimination is compromised in renal insufficiency.

Cephalothin crosses the placental barrier [1, 2, 3, 4, 9, 10], and reaches amniotic fluid and cord blood in therapeutic concentrations [5]. Intravenous or intra-amniotic administration of cephalothin sodium during labour produces

foetal blood concentrations of about 50% of those in the mother [8]. The use of cephalothin in pregnancy is not contra-indicated, because of its low toxicity [3, 4, 10, 11, 14, 15].

Cephalothin does not pass into breast milk [12].

In laboratory animals, cephalothin was not teratogenic [6, 7].

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Cephazolin

Kefzol,

7-(1-(1*H*)-tetrazolylacetamidol)-3-(2-(5-methyl-1,3,4-thiadiazolyl)-thiomethyl)- δ -3-cefem-4-carboxylic acid (MW 476.3)

Not contra-indicated in pregnancy.

Cephazolin is a semi-synthetic antibiotic derived from the natural cephalosporins, active against numerous microorganisms, both Gram-positive and Gram-negative. Its mechanism of action is based on inhibition of biosynthesis of a glycopeptide constituent of the bacterial wall. Cephazolin is not absorbed from the digestive tract. It binds strongly to plasma proteins, and is eliminated in the urine by glomerular filtration and only in small quantities by tubular secretion. It is partly eliminated in the bile, and crosses the blood-brain barrier with difficulty. Cephazolin produces higher blood levels than do other cephalosporins, and has a longer duration of action. Reduced doses should be used in renal insufficiency.

Cephazolin crosses the placental barrier, and reaches foetal blood in concentrations. It is present in amniotic fluid and is eliminated in the urine

during the first few hours of life [1, 5, 7]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3, 4, 6].

Cephazolin passes into breast milk in negligible quantities [1]. Concentrations in milk were unmeasurable following administration of three doses of 500 mg intramuscularly [1].

In the rat, mouse, and rabbit, cephazolin was neither embryofoetotoxic or teratogenic [2].

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Cephaloridine

Ceporin, internal salt of

7-(2-thienyl)acetamido-3-(1-pyridyl-methyl)-3-cefem-4-carboxylic acid (MW 415.5)

Not contra-indicated in pregnancy.

Cephaloridine is a semi-synthetic cephalosporin antibiotic with a wide spectrum of activity, including Gram-positive and Gram-negative bacteria. Its mechanism of action is based on inhibition of the formation of bacterial cell walls. Cephaloridine is only slightly absorbed orally and therefore is used only parenterally. It binds to plasma proteins and is eliminated in the urine. It is slightly nephrotoxic in patients with renal insufficiency.

Cephaloridine crosses the placental barrier [1, 2, 5, 6]. In 70 patients a dose of 1 g cephaloridine every 12 hours for 3 days produced bactericidal concentrations in amniotic fluid in 95% of cases, in cord blood in 75% of cases, and in neonatal serum in 55% of cases. Cephaloridine can be used safely in pregnancy because its toxicity is very low, with good therapeutic results [2, 7]. No embryofoetotoxic or teratogenic effects have been observed.

Cephaloridine was not teratogenic in laboratory animals [3, 4].

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Cephalexin

Ceporex, Keflex,

7- β -(D- α -aminophenylacetamido)-3-methylcefa-3-ene-4-carboxylic acid
(MW 347.24)

Not contra-indicated in pregnancy.

Cephalexin is a semi-synthetic cephalosporin antibiotic with a wide spectrum of action, on both Gram-positive and Gram-negative bacteria. Its mechanism of action is based on inhibition of synthesis of cell wall constituents. Unlike other cephalosporins, it is well absorbed orally. It binds weakly to plasma proteins, and is mainly eliminated in the urine and bile.

Cephalexin crosses the placental barrier, both in the rat [1] and in man [4, 5]. In 8 pregnant women, administration of a single dose produced foetal blood concentrations which were lower than maternal until 4 hours after administration. After 5 hours, however, foetal blood levels were higher than those in the mother [4]. Concentrations in amniotic fluid increased progressively until 7 hours [4]. At therapeutic doses (500 mg four times per day) bacteriostatic levels were reached in foetal blood and amniotic fluid in 50% of cases treated, i.e., 40 patients [5].

In the rat, cephalexin administered orally at a dose of 200 mg/kg crossed the placental barrier, and reached concentrations in the foetus and amniotic fluid 3 hours after administration which were equal to 20% of those in maternal serum [5]. Other authors also demonstrated passage of cephalexin into amniotic fluid [1].

Cephalexin may be used safely at therapeutic doses at all stages of pregnancy [2, 3, 6, 7].

Cephalexin does not pass into breast milk [8].

In the rat and mouse, cephalexin did not affect fertility or viability of the offspring, and it did not affect foetal or neonatal weight gain [1]. In the rat, oral doses of 250–500 mg/kg throughout pregnancy or from the 6th to the 15th day were neither embryofoetotoxic nor teratogenic. Identical results were obtained in the mouse [1].

Cephalexin passed into the milk of the rat and dog, but did not affect the growth of the suckling [1]. In the rat, an oral dose of 25 mg/kg produced after 2 hours a concentration of $\frac{1}{8}$ th that of blood in the milk [1]. In the dog, the same dose after 4 hours produced a concentration in the milk of $\frac{1}{25}$ th that in the blood [1].

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Cephadrine

Velosef,

7-((-)-2-amino-2-(1,4-cyclohexadienyl)-acetamido)desacetoxy-
cephalosporanic acid

Not contra-indicated in pregnancy.

Cephadrine is a semi-synthetic antibiotic derived from cephalosporin, and is active against numerous Gram-positive and Gram-negative bacteria. Its effects are very similar both pharmacologically and clinically to those of cephalixin (see page 345). Cephadrine is actively absorbed from the digestive tract, binds weakly to plasma proteins, and is almost totally secreted in the renal tubules and eliminated in the urine in concentrations which are therapeutically active. Cephadrine is administered orally.

Cephadrine crosses the placental barrier [1,3,5,7,8]. Administered to pregnant women during the 16th–20th weeks, at doses of 2 g/day for at least 2 days, cephadrine was found in the amniotic fluid in concentrations equal to those in maternal serum [1]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3,5,6,8].

In the rat and mouse, cephadrine was neither embryofetotoxic or teratogenic [2,4]. Oral administration of cephadrine in the rat throughout pregnancy at doses of 100–300 mg/kg was without harmful effects [2]. Similar results were obtained in the mouse after administration of the same dose orally from the 6th to the 15th day of pregnancy [4].

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Cephacetrile

(MW 361.31)

Not contra-indicated in pregnancy.

Cephacetrile is a semi-synthetic antibiotic derived from *Cephalosporium acremonium*. Its mechanism of action is based on inhibition of the biosynthesis of constituents of cell walls of many Gram-positive and Gram-negative bacteria. Cephacetrile is administered intramuscularly or intravenously because it is hardly absorbed orally. It is eliminated mainly in the urine, and crosses the blood-brain barrier with difficulty.

Transplacental passage of cephacetrile has been demonstrated, although foetal blood levels are considerably lower than maternal [1]. For this reason, in the event of foetal infection, a therapeutic dose given to the mother is ineffective [1]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [2].

No experimental studies have been described on the use of cephacetrile in pregnancy in laboratory animals.

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Cefuroxime sodium

Zinacef, sodium

3-carbamoyl-oxymethyl-7-(2 Z- α -fur-2-yl- α -methoxy-imino-acetamido)-8-oxo-5-thia-1-azadicyclo(4, 2, 0)oct-2-ene-2-carboxylate (MW 446.4)

Not contra-indicated in pregnancy.

Cefuroxime is a cephalosporin, and is resistant to many endo- β -lactamases produced by Gram-negative bacteria. It is not metabolized. Cefuroxime has a low toxicity, binds weakly to plasma proteins, has a half life of 1 hour and is totally excreted in the urine.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1].

In the mouse and rabbit, cefuroxime had no embryofoetotoxic or teratogenic effects [2]. In the mouse, administration of the drug at a dose of 64000 mg/kg/day from the 6th to the 15th day of pregnancy was harmless [2]. In the rabbit, administration of cefuroxime at a dose of 400 mg/kg/day from the 6th to the 18th day of pregnancy was without harmful effects [2].

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Cefoxitin sodium

Mefoxin, sodium salt of

3-(hydroxymethyl)-7- α -methoxy-8-oxo-7(2-(2-thienyl)-acetamido)-5-thia-1-aza bicyclo-(4, 2, 0)oct-2-ene-2-carboxylate carbamate (MW 449.44)

Not contra-indicated in pregnancy.

Cefoxitin is a new semi-synthetic cephalosporin belonging to the cefamycine family. Its fundamental pharmacological characteristic is that of high resistance to the action of the cephalosporinases, because of the presence of the thienylacetic group which substitutes that of the amino-adipic group. The drug has a wide spectrum of activity on both Gram-positive and Gram-negative bacteria, with inhibition of synthesis of the cell walls, resulting in a bacteriocidal effect. The effectiveness of cefoxitin against some Gram-negative aerobes such as *Proteus mirabilis*, *Serratia marcescens*, and anaerobes such as *Bacteroides fragilis* should be emphasized. Among the bacteria resistant to cefoxitin are certain strains of *Pseudomonas* and many strains of *Enterococci*.

Cefoxitin crosses the placental barrier [3]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. We maintain that this drug is not contra-indicated in pregnancy, by analogy with other cephalosporins, and the manufacturers concur with this view [1], although no control studies on the effects of cefoxitin in pregnancy have been carried out.

Cefoxitin passes into breast milk [2]. After intravenous administration of 1 g, the concentration in maternal milk after 2 hours was 5.6 mg/l.

In the mouse and rabbit, cefoxitin was neither embryofetotoxic nor teratogenic [1]. In the mouse, parenteral doses of 100–300–900 mg/kg from the 6th to the 15th day of pregnancy were not teratogenic, and did not affect the incidence of abortions or the number or weight of the embryos when compared to controls [1]. In the rabbit, the same doses administered for the same period gave similar results [1].

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1.6 Rifampicin

The rifampicins are antibiotics with a macrocyclic structure, and are effective against Gram-positive and Gram-negative bacteria, as well as against tubercular mycobacteria. They inhibit the DNA-dependent RNA-polymerase enzyme, and thus the synthesis of RNA in microorganisms. The rifampicins have moderate hepatotoxicity, and produce gastrointestinal effects and lethargy. The following drugs are discussed here:

	Recommendation	Page
Rifamicin	P	349
Rifampicin	P	350

During pregnancy the rifampicins cross the placental barrier. No contraindications to their use in pregnancy have so far appeared in the literature, even in the first trimester.

Rifamicin

rifamicin sodium (MW 697.8)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Rifamicin is an antibiotic produced by *Streptomyces mediterranei*, and is active against certain Gram-positive and Gram-negative bacteria, and also against tubercular mycobacteria. Its mechanism of action is based on the inhibition of RNA polymerase, and thus it prevents the synthesis of bacterial RNA. If this enzyme system can be modified, resistance to the antibiotic develops. Rifamicin is used in association with other drugs in initial therapy of pulmonary tuberculosis and in other bacterial infections.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,4,5,6]. However, we advise care in the use of rifamicin in pregnancy (see rifampicin, page 350).

In the rat and mouse, rifamicin was teratogenic, but in the rabbit, it produced no harmful effects [2]. In the mouse and rat, oral doses above 150 mg/kg during the period of organogenesis caused spina bifida in both species and cleft palate in the mouse [2]. Similar treatment in the rabbit did not affect the foetus [2].

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Rifampicin

Rimactane, Rifadin, Rimactazid, Rifinah,

3-(4-methyl-1-piperaziny-1-iminomethyl) rifamycin (MW 822.54)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

In the USA, rifampicin is known as rifampin. It is a semi-synthetic antibiotic derived from rifamycin D, produced by *Streptomyces mediterranei*. It inhibits the RNA-polymerase of mycobacteria and other Gram-positive and Gram-negative microorganisms, but not that of animal cells. Rifampicin is moderately toxic in the liver (jaundice) and the medulla (anaemia, leucopenia, thrombocytopenia). It is used to treat tuberculosis and other infections.

Rifampicin crosses the placental barrier [1, 2, 3, 9, 16, 27]. Administered to the mother at a dose of 400 mg, 4 hours before therapeutic abortion, the drug was found in foetal blood at a level of 0.6 ng/ml, in amniotic fluid at 0.1 ng/ml, and in maternal blood at 2.6 ng/ml [27]. The effects of administration of rifampicin in pregnancy are controversial. Some authors maintain that the drug is completely safe [4, 5, 6, 7, 8, 9, 10, 11, 12, 29, 30], while others believe that its use, particularly in the first trimester of pregnancy, should be contra-indicated [13, 14, 15, 25, 28]. Some authors think that prolonged treatment with rifampicin in women of childbearing age who are likely to conceive should be associated with contraceptive treatment, but unfortunately rifampicin antagonizes the action of oral contraceptives [7, 20, 21, 22, 23, 24], and therefore this idea may not be practicable.

A retrospective study of 182 pregnant women treated with rifampicin and/or ethambutol showed no embryofetotoxic effects with either drug [8]. In another investigation, 40 pregnant women were treated with rifampicin with no harm to the foetus [5], and two other cases of normal foetal development followed rifampicin treatment in the first trimester [6]. A patient who was being treated with 300 mg/day of isoniazid, 800 mg/day of ethambutol, and 600 mg/day of rifampicin for pulmonary tuberculosis became pregnant on two occasions, although she was taking oral contraceptives. The first pregnancy was interrupted by the wish of the patient, the second resulted in the birth of a healthy infant [7]. In another study, 147 pregnant women were treated with rifampicin in combination with ethambutol, cycloserine, and isoniazid. The incidence of neonatal malformations was no greater than that of controls. It should be stressed that 82 of these patients had taken rifampicin during the period of organogenesis [4]. Three cases of haemorrhage in infants who were

born to patients treated in pregnancy with rifampicin, ethanbutol, and/or isoniazid were described. It was believed that the drug could interfere with the synthesis of prothrombin because of its ketone structure, similar to that of vitamin K [15]. One pregnant woman was treated for chronic pyelonephritis with rifampicin at doses of 1200 mg/day. Following the birth, there were disturbances in hepatic function and blood coagulation in both mother and infant [14].

In the rat, mouse, and rabbit, rifampicin was embryofetotoxic at high doses (ten times greater than therapeutic), while at doses of about 100 mg/kg it did not affect normal reproduction [17, 26]. In the rat, doses of 100 mg/kg from the 6th to the 16th day of pregnancy were neither embryofetotoxic nor teratogenic. A dose of 150–200 mg/kg at various stages of gestation was embryofetotoxic and teratogenic (spina bifida) [26]. In the mouse, oral doses of 50–100 mg/kg did not affect embryogenesis, while doses of 150–200 mg/kg caused resorption, cleft palate, and spina bifida [26]. In the rabbit, a dose of 50–200 mg/kg was embryotoxic (200 mg/kg) but not teratogenic [5].

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1.7 Chloramphenicol

Chloramphenicol is a wide-spectrum antibiotic which is also active against the rickettsiae and the mycoplasmas, and acts like the macrolides and lincomycin in inhibiting bacterial synthesis. Its numerous side effects, which have been widely described in the literature, limit its use to cases of proven therapeutic necessity, in which other potentially less harmful antibiotics would be ineffective. Thiamphenicol, a less toxic synthetic derivative, has a similar antibacterial spectrum. The following drugs are discussed in this section:

	Recommendation	Page
Chloramphenicol	C	352
Thiamphenicol	P	355

In pregnancy, chloramphenicol is contra-indicated because it crosses the placental barrier, accumulates in the foetus, and is not readily metabolized. Thiamphenicol may be used with fewer reservations.

Chloramphenicol

Actinac, Chlormycetin, Minims, Opulets, Otopred (MW 323.14)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				C	
Chronic		C	C		C

Contra-indicated in pregnancy and during lactation.

Chloramphenicol is an antibiotic produced by *Streptomyces venezuelae*, obtained by synthesis as a result of its relatively simple chemical structure. It has both bacteriostatic and bacteriocidal actions on numerous Gram-negative organisms and on the rickettsiae. Chloramphenicol is an inhibitor of protein synthesis not only in bacteria but also in animal cells. It is rapidly absorbed, penetrates all tissues and biological fluids (amniotic fluid, bile, milk, etc.), and is inactivated by glucuronide conjugation and then rapidly eliminated in the urine. Its principal side effect is bone marrow aplasia, with anaemia, leucopenia, and thrombocytopenia.

In neonates, especially when premature, therapy with chloramphenicol

may lead to fatalities (the so-called 'gray syndrome') following overdosage. Elimination of the drug is reduced because of the inadequacy of renal function and hepatic glucuronide conjugation. For this reason, chloramphenicol should be avoided where other drugs could be used.

Chloramphenicol crosses the placental barrier. Foetal plasma levels may reach 25–100% of those in the mother [1,2,3,4,5,32,34,38,42,43]. In amniotic fluid, chloramphenicol may reach levels which according to some authors [5] are negligible and according to others [6] are high.

Some authors [19,44,46] believe that chloramphenicol has no embryo-foetotoxic actions, and is therefore not contra-indicated in pregnancy. Others, however [32,33,39,42], believe that the drug should be used with care in pregnancy because of the possibility of its accumulation in the free form, which is active and toxic, in foetal blood because of the inefficiency of glucuronide conjugation in the foetus.

When birth is imminent, administration of chloramphenicol to the mother at therapeutic doses may cause an accumulation of the drug in the neonate, with the resultant 'gray syndrome' [7,8,9,10,11,12,35,40,41,44,45,47,48]. Chloramphenicol also passes into breast milk [15,17,36], reaching concentrations equal to 50% of those in the serum [13]. Use of the drug is therefore contra-indicated during lactation since it may provoke symptoms of overdosage in the nursing infant. Administered to nursing mothers, an oral dose of 250 mg can lead to the appearance in the milk of 2.5%, while that in maternal serum was 4.9% [13]. Other authors [15], using biological methods, were unable to find traces of chloramphenicol in milk after administration of 3–4 g. Some authors believe that the drug is eliminated in the milk in a biologically inactive form [17]. In their view, there is no need for chloramphenicol to be contra-indicated during lactation.

In the mouse, rabbit, and macaque mulatto, chloramphenicol was embryotoxic but not teratogenic, while in the rat and chick embryo, it was teratogenic. Investigations in the guinea-pig have shown rapid passage of chloramphenicol into foetal blood and amniotic fluid. The concentration in the latter was not therapeutic [31]. Chloramphenicol has also been found in the amniotic fluid of the rat [37].

In the mouse, oral doses of 0.5–2 g/kg in a single administration from the 5th to the 15th day of pregnancy were embryofoetotoxic [18]. In the rat, doses of 100–200 mg/kg during pregnancy were not teratogenic [24], while oral doses of 2.5 g/kg from the 9th to the 11th day of pregnancy were teratogenic, causing cleft palate [20]. Subcutaneous doses of 0.7–1.2 g/kg from the 6th to the 10th day of pregnancy were embryofoetotoxic and teratogenic (hydronephrosis) [21]. Oral doses of 0.5–2 g/kg in a single administration from the 5th to the 17th day of pregnancy caused gastroschisis [18]. Chloramphenicol added to the diet (2–4%) during the second half of pregnancy produced generalized oedema in the foetus [22].

In the rabbit, intramuscular doses of 300 mg/kg from the 11th to the 19th day of pregnancy or an oral dose of 1 g/kg in a single administration from the 6th to the 11th day of pregnancy were embryofetotoxic but not teratogenic [18,25,26].

Chick embryos treated with concentrations of 0.2 mg/ml chloramphenicol for 6 hours developed microcephalus and cardiac malformations [27]. Other authors have reported malformations of the splanchnopleura and of the central nervous system [28,29]. In the macaque mulatto, chloramphenicol was not teratogenic [30].

The rate of passage of chloramphenicol across the placental barrier has been studied in the guinea-pig. Oral administration of 100 mg/kg produced a concentration in maternal plasma of 10 µg/ml within 2 hours, while the same concentration was reached in foetal blood in 30 minutes [31]. In three cases, the presence of chloramphenicol was demonstrated in amniotic fluid at doses effective in treatment of amniotic infection [31].

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Tiamphenicol

D-*d*-threo-1-(*p*-methylsulphonylphenyl)-2-dichloroacetamido-3-amino-acetoxy-1-propanol hydrochloride (MW 356.23)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic		P	P		

To be used with care in pregnancy.

Tiamphenicol is a derivative of chloramphenicol, and is not metabolized, but eliminated unchanged in the urine.

Tiamphenicol crosses the placental barrier. After intravenous administration of 500 mg, foetal plasma and amniotic fluid concentrations remain lower than those in maternal plasma, although they are still therapeutically active [1,8]. No foetal malformations have been reported following the use of tiamphenicol in pregnancy, but since the drug interferes with protein synthesis, it would be safer to avoid its use in the first trimester [2,9]. Tiamphenicol has been used after the first trimester, particularly in the treatment of pyelonephritis, with excellent results [3,4,5], and with no harmful effects on the foetus, in contrast to chloramphenicol (see page 352).

In the mouse, rat, and rabbit, tiamphenicol was embryofetotoxic at high doses but not teratogenic [6,7]. In the mouse, subcutaneous doses of 2-5-20-50 mg/kg did not produce malformations or toxic effects [6]. Intraperitoneal doses of 30-400-700 mg/kg from the 7th to the 12th day of pregnancy were foetotoxic at the higher doses but not teratogenic [7].

In the rat, subcutaneous doses of 25-50-75-150 mg/kg were not teratogenic, but they did cause an increase in foetal resorption at a dose of 75 mg/kg

[6]. Intraperitoneal doses of 25–50–100 mg/kg from the 9th to the 14th day of pregnancy were embryofetotoxic at the higher doses but not teratogenic [7]. Oral doses of 40–80–160 mg/kg at various stages of pregnancy were not teratogenic [9].

In the rabbit, oral doses of 50–80 mg/kg from the 8th to the 16th day of pregnancy caused toxic effects (increase in foetal resorption in the group treated with the highest dose), but were not teratogenic [9]. The same results were obtained with oral doses of 100–150 mg/kg during the period of organogenesis [2].

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1.8 Other antibiotics

In this group, various drugs are included which have varying chemical structures, mechanisms of action, and antibacterial spectra. They are not in current use, or are used only for very specific indications. For example, cycloserine and viomycin are used to treat tuberculosis which is resistant to other drugs, spectinomycin and pristinomycin are used in the therapy of gonorrhoea, lincomycin and vancomycin are used in the treatment of Gram-negative infections. The following drugs are discussed in this section:

	Recommendation	Page
Lincomycin	NC	357
Clindamycin hydrochloride	NC	358
Cycloserine	P	358
Vancomycin hydrochloride	P	359
Phosphomycin	NC	360
Novobiocin	C	361
Spectinomycin	NC	362
Viomycin sulphate	C	363
Capreomycin sulphate	C	364
Pristinomycin	NC	364

During pregnancy, lincomycin and spectinomycin, which act respectively on Gram-positive and Gram-negative organisms, are not contra-indicated. Cycloserine and vancomycin, antitubercular antibiotics, should be used with care because of possible embryofoetotoxicity. Pristinomycin, active against particular gonococci, is not contra-indicated. Novobiocin, which interferes with processes of glucuronide conjugation, is contra-indicated in the last part of pregnancy.

Lincomycin

Lincocin,

methy1-6,8-di-desoxy-6-(1-methyl-4-propyl-2-pyrrolidine-carboxamido)-1-thio-D-erythro-D-galacto-8-pyranoside hydrochloride (MW 461.0).

Not contra-indicated in pregnancy.

Lincomycin is an antibiotic produced by an actinomycete, *Streptomyces lincolnensis*, active against many Gram-positive bacteria. It attaches to bacterial ribosomes, inhibiting protein synthesis. Lincomycin is used principally in the therapy of infections caused by *pyogenes* and in osteomyelitis.

Lincomycin crosses the placental barrier [1,2]. Administered intramuscularly to 60 mothers at a dose of 600 mg before artificial rupture of the membranes, the concentration of the drug in cord blood was about one third that of maternal blood [1]. Lincomycin has been used in pregnancy for the treatment of cervicitis and vaginitis without embryofoetotoxic or teratogenic effects [3,4,5]. Lincomycin was administered to about 300 patients at various stages of pregnancy, including the first trimester, at doses of 2 g/day for 7 days. No increase was reported in foetal or perinatal complications, nor were there any malformations [4].

In the rat and dog, lincomycin had no embryofoetotoxic or teratogenic effects, nor was its transplacental passage demonstrated [6]. In the rat, subcutaneous doses of 75 mg/kg for two reproductive cycles did not cause embryofoetotoxic or teratogenic effects [5]. In the dog, doses of 50 mg/kg throughout pregnancy were not teratogenic [6]. Although lincomycin passed into the milk, it had no adverse effects on the sucklings [6].

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Clindamycin hydrochloride

Dalacin C,

methyl-7-chloro-6,7,8-trideoxy-6-*trans*-(1-methyl-4-propyl-L-pyrrolidino-2-carboxamido)-1-thiol-L-threo- α - δ -galacto-octapyranoside hydrochloride (MW 461.4)

Not contra-indicated in pregnancy.

Clindamycin is a derivative of lincomycin, from which it differs by having a greater antibacterial activity and because of greater intestinal absorption. It has a shorter plasma half-life (little more than 2 hours). Clindamycin is more than 90% bound to plasma proteins, and is distributed in all tissues, but does not reach the central nervous system. It tends to accumulate if there is hepatic or renal insufficiency, and may provoke colitis with diarrhoea, nausea, vomiting, abdominal pains, and a reversible increase in transaminases and alkaline phosphatases in the serum. Clindamycin is excreted in the urine (10%) and in the faeces (4%).

Clindamycin crosses the placental barrier by facilitated diffusion, and is found in amniotic fluid. It also concentrates in foetal liver [1], particularly after administration of multiple doses. For this reason, clindamycin is useful in the therapy of uterine infection [1, 3].

In the mouse and rat, clindamycin was neither embryofoetotoxic nor teratogenic [2]. Subcutaneous administration of the drug at doses of 100–180 mg/kg from the 5th to the 15th day of gestation did not affect reproduction or cause teratogenic effects [2].

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Cycloserine

D-4-amino-3-isoxazolidone (MW 102.09)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Cycloserine is an antibiotic with antitubercular activity, effective against strains resistant to other antibiotics. It probably acts by blocking protein synthesis in the bacterial cell walls. Cycloserine has toxic side effects in the

central nervous system (depression, anxiety, convulsions), which are attenuated by pyridoxine.

Cycloserine crosses the placental barrier [1,2,3,4] and reaches the same concentrations in maternal blood, foetal blood, and amniotic fluid [11,12]. Its use in pregnancy does not produce teratogenic effects [9,15]. Other authors, however, advise against administration of cycloserine in pregnancy, claiming that its safety has not been sufficiently proved. We believe that it should be used with care in pregnancy.

Cycloserine passes into breast milk [13].

In the chick embryo, cycloserine can be teratogenic, causing skeletal anomalies [10].

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Vancomycin hydrochloride

Vancocin (MW 3296.03)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Vancomycin is an antibiotic produced by *Streptomyces orientalis*, and possesses bactericidal action, particularly against Gram-positive organisms. Its mechanism of action has not yet been established, but it is thought to inhibit the biosynthesis of mucopolysaccharides in the cell walls. After oral administration it is only slightly absorbed. For systemic therapy, it is necessary to use the intravenous route. Vancomycin can be ototoxic and nephrotoxic. It is used mainly in staphylococcal infections which are resistant to other antibiotics.

Vancomycin crosses the placental barrier [1, 6], although this was previously doubted [2]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3, 4, 5]. However, the toxicity of vancomycin, and the lack of clinical experience in its use, leads us to advise care in its use in pregnancy.

No experimental studies have been described on the use of vancomycin in pregnancy in laboratory animals.

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Phosphomycin

cis-1,2-epoxypropyl phosphoric acid(—) (MW 138.1)

Not contra-indicated in pregnancy.

Phosphomycin is an antibiotic produced by a strain of *Streptomyces fradiae*, but is actually obtained by synthesis. The molecule has two characteristics, an epoxide group which is responsible for the antibacterial activity, and a direct phosphorus—carbon link, which is unusual in an organic substance. Its low molecular weight facilitates its passage through biological membranes.

Phosphomycin penetrates bacterial cells by means of a specific transport system, and inhibits the initial phases of synthesis of cell walls, having bacteriocidal activity on microorganisms in the replication phase. The similarity of this antibiotic to phosphoenol pyruvate allows it to block pyruvyl transferase activity, thus impeding the utilization of acetylglucosamine for the biosynthesis of the peptidoglycans, polymers which confer rigidity on bacterial cell walls. This elective action does not interfere with metabolism of animal cells, in which phosphoenol pyruvate is used in a different way. Phosphomycin does not bind to plasma proteins, and thus has a high bio-availability. It is distributed in an apparent volume of about 20 litres, which represents more than the total extracellular fluid volume, and this implies that it enters the cells and passes into the lymph, bronchial secretions, and exudates. Phosphomycin is metabolized in the liver and kidneys, but is not taken up by enterohepatic recirculation. Its plasma half life is about 2 hours. Excretion is mainly by glomerular filtration without tubular reabsorption. Renal and hepatic toxicity are very low. The antibacterial activity of phosphomycin is against numerous Gram-positive and Gram-negative organisms, and there are very few resistant strains.

Phosphomycin crosses the placental barrier [1, 2]. A pharmacokinetic study in labour has demonstrated that in foetal blood, concentrations are reached which are equal to those in maternal blood after 160–200 minutes, and that there is a close correlation between these two levels and total foetal concentration and placental weight [2]. In amniotic fluid, phosphomycin levels are equal to maternal blood levels, and the drug is eliminated in the lochia and to a small degree in colostrum and milk [1]. Phosphomycin is thus useful in uterine infection, and can effectively protect the foetus.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [4], and the manufacturers concur with this view [3].

Phosphomycin passes into breast milk [4].

In the mouse, rat, and rabbit, phosphomycin was neither embryofoetotoxic nor teratogenic [4, 5, 6]. In the mouse, oral doses above 240 mg/kg/day during the period of organogenesis were harmless [4]. In the rabbit, intravenous doses greater than 240 mg/kg/day during the same period were likewise without harmful effects [4]. Intravenous doses of 28.5–57 mg/kg/day from the 9th to the 18th day of pregnancy had no adverse effects [5]. In the rat, oral doses of 150 mg/kg/day administered before, during mating, and during pregnancy and lactation were not embryofoetotoxic and did not affect reproduction [5].

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Novobiocin

Albamyin T,

7-(carbamoyltetrahydro-3-hydroxy-5-methoxy-6, 6-dimethylpyran-2-yloxy)-4-hydroxy-3,(4-hydroxy-3-(3-methylbut-2-enyl)-benzamido)-8-methyl-2*H*-chromen-2-one (MW 612.65)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			C	C	
Chronic					

Contra-indicated in late pregnancy and during labour.

Novobiocin is an antibiotic, and is active against Gram-positive bacteria and some Gram-negative organisms. Its use has been almost completely abandoned

because of its toxicity (cutaneous eruptions, fever, diarrhoea, leucopenia, thrombocytopenia, eosinophilia) [1].

Novobiocin crosses the placental barrier in small quantities [2,10]. Administration immediately before birth can interfere with conjugation of bilirubin with consequent neonatal jaundice [3,4,9,11]. With regard to its administration in pregnancy, no reports have been found of harmful effects on the mother or the foetus.

Novobiocin passes into breast milk in small quantities, but is not contra-indicated during lactation [5,9]. Following an initial dose of 500 mg, and subsequent doses of 250 mg every 6 hours, novobiocin was found in breast milk to the extent of 0.36–0.54% from 6 to 30 hours after administration [5].

No experimental studies have been described on the use of novobiocin in pregnancy in laboratory animals.

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Spectinomycin

Trobicin,

decahydro-4*a*,7,9-trihydroxy-2-methyl-6,8-di(methylamino)-4*H*-pyran-(2,3*b*) (1,4)benzodioxin-4-one (MW 332.4)

Not contra-indicated in pregnancy.

Spectinomycin is an antibiotic produced from *Streptomyces spectabilis*, and it inhibits protein synthesis in the ribosomes of Gram-negative bacteria, thus having a bacteriostatic effect. Its pharmacological action is mainly on gonococci. It is administered exclusively by the intramuscular route, does not bind to plasma proteins, and is eliminated unchanged in the urine. Spectinomycin can cause anaemia and an increase in serum transaminases. It is used only in the treatment of gonococcal infections.

The clinical use of spectinomycin so far does not suggest that it should be contra-indicated in pregnancy. There are no reported adverse effects in the literature.

In laboratory animals, spectinomycin was neither embryofoetotoxic nor teratogenic [1,2,3,4].

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Viomycin sulphate

(MW 685.71)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Viomycin sulphate is an antibiotic with a polypeptide structure, obtained from a strain of *Streptomyces*. It has a bacteriostatic action against *Mycobacterium tuberculosis*, including those strains resistant to streptomycin and to isoniazid. Resistance may also be developed towards viomycin, but this is delayed by the simultaneous administration of other antitubercular drugs. Viomycin is ototoxic and nephrotoxic, and should be used only when resistance to first-line antitubercular drugs has developed.

Passage through the placenta seems to be very slow, although this may depend in part on the route of administration (poor absorption through the intestinal wall) [3]. Administration of viomycin in pregnancy has been shown to be teratogenic [1,2].

In the rat, viomycin was embryofoetotoxic and teratogenic [4,5]. A subcutaneous dose of 1400–2800 mg/kg from the 6th to the 10th day of pregnancy caused retardation of growth, increase in foetal resorption, and malformations of various organs [4].

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Capreomycin sulphate

Capastat (MW 740.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Capreomycin is a bacteriostatic and antimycobacterial agent with a cyclic peptide structure, analogous to viomycin (page 363), produced by some strains of *Streptomyces capreolus*. Besides causing hypocalcaemia, hypopotassaemia, leucopenia or leucocytosis, eosinophilia, fever, and cutaneous rashes, capreomycin is hepato-nephro-ototoxic.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. It has been shown that capreomycin at concentrations of 0.015 mg/ml did not induce chromosomal lesions in cultured leucocytes *in vitro* [3]. However, we maintain that the drug should be contra-indicated in pregnancy because of its structural similarity to viomycin, and because there is insufficient information available on its use in pregnancy.

In the rat, administration of capreomycin in pregnancy was neither embryo-foetotoxic nor teratogenic [1, 2]. Administration of the drug to 40 rats subcutaneously at doses of 50–100 mg/kg at the beginning of pregnancy did not significantly increase foetal resorptions or malformations [2].

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Pristinomycin

(MW 866.95)

Not contra-indicated in pregnancy.

Pristinomycin is an antibiotic which is extracted from a filtrate of *Streptomyces pristina spiralis*, active principally against staphylococci, haemolytic streptococci, and pneumococcus. It is also effective against some Gram-negative bacteria and in particular gonococcus.

No reports have been found of harmful effects on the human foetus, the mother or the pregnancy [1, 2]. Oral administration of pristinomycin at a dose of

1–2 g/day to 4 pregnant women from the 8th month of pregnancy onwards did not cause any side effects in the mother or the foetus [2].

No experimental studies have been described on the use of pristinomycin in pregnancy in laboratory animals.

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2. SULPHONAMIDES

The sulphonamides may be distinguished on the basis of their pharmacodynamic properties, absorption, and elimination. Some are rapidly absorbed and eliminated, others are rapidly absorbed and slowly eliminated, while still others are not absorbed from the digestive tract. The sulphonamides compete with para-aminobenzoic acid which is essential for the biosynthesis of folates in certain bacterial species. In addition to their well-known use as bacteriostatics, the sulphonamides also have a diuretic action (see thiazides and inhibitors of carbonic anhydrase, page 2), and are hypoglycaemic (see sulphonylurea, page 370). The following drugs are discussed in this chapter:

	Recommendation	Page
<i>Sulphonamides, rapidly eliminated</i>		
Sulphanilamide	NC (P before parturition)	367
Sulphafurazole	NC (P before parturition)	368
Sulphacarbamide	NC (P before parturition)	370
Sulphachlorpyridazine	NC (P before parturition)	370
Sulphamethazole	NC (P before parturition)	371
<i>Sulphonamides, slowly eliminated</i>		
Sulphamethoxypyridazine	NC (P before parturition)	372
Sulfalene	NC (P before parturition)	373
Sulphadimethoxyine	NC (P before parturition)	375
Sulphadimidine	NC (P before parturition)	376
Sulphamethoxydiazine	NC (P before parturition)	377
Sulphadoxin	NC (P before parturition)	379
Sulphamoxole	NC (P before parturition)	380
Sulphaphenazole	NC (P before parturition)	381
Sulfaperine	NC (P before parturition)	382
<i>Sulphonamides with slight intestinal absorption</i>		
Phthalylsulphathiazole	NC (P before parturition)	383
Sulphaguanidine	NC	384
Salazosulphapyridine	P	384
<i>Sulphonamides in association</i>		
Sulphamethoxazole + trimethoprim	NC (P before parturition)	385

In pregnancy the sulphonamides with systemic action and rapid or slow elimination are contra-indicated only in the last part of pregnancy, particularly close to birth, because they may cause neonatal jaundice. The slightly soluble sulphonamides, those with slight intestinal absorption, have no such limitations. Salazosulphapyridine should be used with care because of the salicylate component. The combination of sulphamethoxazole and trimethoprim should not be used near to birth.

2.1 Sulphonamides, rapidly eliminated

Sulphanilamide

Rhinamide,

p-amino-benzene sulphonamide (MW 172.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated during pregnancy, but should be used with care close to birth.

Sulphanilamide is the original sulphonamide drug, and is characterized by bacteriostatic action as a result of competition with para-aminobenzoic acid. Only those bacterial strains which utilize this substance for the biosynthesis of folic acid are sensitive, while those which, like animal cells, do not synthesize folic acid are resistant.

The water-soluble sulphonamides are rapidly absorbed from the digestive tract, are partly bound to plasma proteins, are distributed in all tissues and biological fluids, and are metabolized by oxidation and acetylation in the liver. They are largely excreted in the urine. The rate of absorption and elimination varies from drug to drug. These factors are important in deciding which substance to use in particular cases. Those which are very water-soluble are used in the therapy of infections of the urinary tract, those rapidly absorbed but slowly eliminated (so-called 'low dose') are used in systemic infections, while the moderately water-soluble ones are used in intestinal infections. Hypersensitivity to the sulphonamides may give rise to a series of haematological changes (anaemia, agranulocytosis, thrombocytopenia) and liver damage (jaundice, hepatocellular damage, even to the point of acute yellow atrophy).

Sulphanilamide, like all sulphonamides, crosses the placental barrier [1,2,3,4,5,6,7,8,9,10,11,12,13,14]. Although there are occasional references in the literature to teratogenicity, probably related to the use of sulphonamides in pregnancy [15,16,17], sulphanilamide is not contra-indicated, because it is

rapidly eliminated, and is unlikely to accumulate in the foetus [3,11,18,19]. Some authors, however, maintain that even with sulphonamides which are rapidly eliminated, care should be exercised immediately before birth because of the danger of neonatal jaundice [14,20,24,25,26].

Sulphanilamide passes into breast milk [21,22].

In the rat and mouse, sulphanilamide was neither embryofoetotoxic nor teratogenic [23]. In the rat, an oral dose of 1–2 g/kg from the 9th to the 14th day of pregnancy was without harmful effects [23]. In the mouse, oral doses of 1 g/kg from the 7th to the 12th day of pregnancy were likewise harmless [23].

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Sulphafurazole or sulphisoxazole

Gantrisin, 3,4-dimethyl-5-sulphanilamido-isoxazole (MW 267.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before parturition.

Sulphafurazole is rapidly absorbed and metabolized. It is effective against Gram-positive and Gram-negative bacteria, in particular against *Proteus* and *Escherichia coli*. For further information, see sulphanilamide (page 367).

Transplacental passage of sulphafurazole has been demonstrated [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 24]. Although there have been a few cases reported in the literature of teratogenicity linked to sulphonamides in pregnancy [14, 15, 16], sulphafurazole is not contra-indicated, because it is rapidly eliminated and does not accumulate in the foetus [3, 11, 17, 18]. Some authors, however, maintain that even with such sulphonamides, care should be exercised just before birth to avoid the danger of possible neonatal jaundice. Several cases of neonatal jaundice have been described following the use of rapidly acting sulphonamides in the last trimester [19, 20, 21].

Sulphafurazole passes into breast milk [22].

In the rat and mouse, sulphafurazole was embryofoetotoxic and teratogenic [23]. In the rat, oral doses of 1 g/kg from the 9th to the 14th day of pregnancy were embryofoetotoxic and teratogenic [23]. In the mouse, similar doses from the 7th to the 12th day of pregnancy had harmful effects [23].

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Sulphacarbamide or sulphonylurea

✓ Uromide, *p*-aminobenzene sulphonylurea (MW 215.23)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before parturition,

Sulphacarbamide is a bacteriostatic, effective mainly in controlling organisms involved in urinary tract infection.

Transplacental passage of sulphacarbamide has been shown even during the first trimester [1,7]. After passing the placental barrier, foetal blood levels are between 50 and 90% of those in maternal blood [7]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, although some authors advise care in the use of sulphacarbamide just before parturition [2,3].

In the rat, at very high doses, sulphacarbamide was foetotoxic but not teratogenic [4]. Doses of 1 g/kg on the 10th day of pregnancy resulted in foetal resorption in 44% of cases [4].

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Sulphachlorpyridazine

3-sulphanilamido-6-chloropyridazine (MW 284.74)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated during pregnancy, but should be used with care before parturition.

Sulphachlorpyridazine is a wide-spectrum antibiotic, and is used particularly in infections of the urinary tract, from which it is slowly eliminated.

Sulphachlorpyridazine crosses the placental barrier, and blood levels in the foetus lie between 50 and 90% of those found in maternal blood [4]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, although some authors advise care in its use immediately before birth, to avoid the danger of neonatal jaundice [1, 2].

The drug has been used at doses of 500 mg/day in asymptomatic bacteriuria in 11 patients in the last 4 months of pregnancy and up to two weeks before birth, without any damaging effects to the mother or to the foetus [3].

No experimental studies have been described on the use of sulphachlorpyridazine in pregnancy in laboratory animals.

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Sulphamethazole

2-sulphanilamido-5-methyl-1, 3, 4-thiadiazole (MW 270.33)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before parturition.

Sulphamethazole is a thiodiazole derivative, and is very soluble, which makes it useful in the treatment of urinary infections. It is characterized by rapid absorption from the gastrointestinal tract, undergoes slight acetylation, and is rapidly excreted in the urine.

Sulphamethazole crosses the placental barrier, and blood levels in the foetus lie between 50 and 90% of those in the mother [2, 4, 5, 6, 7, 8, 9]. Although no reports have been found of harmful effects on the foetus, the mother, or the pregnancy, some authors advise care in the use of this drug immediately before birth, to avoid the danger of neonatal jaundice [10, 11, 12].

No experimental studies have been described on the use of sulphamethazole in pregnancy in laboratory animals.

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2.2 Sulphonamides, slowly eliminated

Sulphamethoxypyridazine

Lederkyn, 3-sulphonamido-6-methoxypyridazine (MW 280.32)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before parturition.

Sulphamethoxypyridazine is a long-acting sulphonamide which is used principally in infections of the urinary tract. For further information, see sulphanilamide (page 367).

Sulphamethoxypyridazine crosses the placental barrier [1,2,3,4,5,6,7,8,9,10,11,12,13,28,29,33,34,35,36]. Although there are only occasional references in the literature to teratogenic effects linked to the administration of long-acting sulphonamides in pregnancy, there are, however, retrospective studies [14,15,16] which confirm that sulphamethoxypyridazine is not contra-indicated [3,4,9,12,13,21,22,28,30]. The drug should be used with care immediately before parturition, to avoid possible danger of neonatal jaundice [2,3,4,6,7,8,9,12,13,17,18,19,20,21,23,24,28,31,35,37,38].

Sulphamethoxypyridazine passes into breast milk [32].

In the rat and mouse, sulphamethoxypyridazine was embryofoetotoxic and teratogenic [25], as are other sulphonamides [13,22,26,27]. In the rat, oral doses of 200–500 mg/kg from the 9th to the 14th day of pregnancy had harmful effects [25]. In the mouse, oral doses of 1 g/kg from the 7th to the 12th day of pregnancy caused malformations of the urogenital tract [25].

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Sulfalene or sulphamethopyrazine

2-sulphanilamido-3-methoxyypyrazine (MW 280.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care immediately before birth.

Sulfalene has a wide spectrum of activity and a long duration of action. It is used to treat respiratory and urinary infections. For further information, see sulphanilamide (page 367).

Transplacental passage of sulfalene has been demonstrated in man [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28] and in animals [29]. Although occasional references have been made in the literature to teratogenic effects linked to the use of long-acting sulphonamides in pregnancy [14, 15, 16], sulfalene is not contra-indicated [3, 4, 9, 12, 13, 21, 22, 28]. It should, however, be used with care immediately before parturition to avoid the danger of possible neonatal jaundice, particularly in premature infants [2, 3, 4, 6, 7, 8, 9, 12, 13, 17, 18, 19, 20, 21, 23, 24, 28, 33].

In laboratory animals, sulfalene was embryofetotoxic and teratogenic [30, 31, 32], as are other sulphonamides [13, 22, 25, 26, 27]. In the rat, doses of 50 mg/kg during the period of organogenesis were fetotoxic [30]. Doses of 200 mg/kg were also teratogenic [30]. Oral doses of 500–700 mg/kg from the 9th to the 14th day of pregnancy were embryofetotoxic and teratogenic [31]. Doses of 100–500 mg/kg throughout pregnancy or during the latter half were not teratogenic [32]. In the mouse, oral doses of 1–2 g/kg from the 7th to the 12th day of pregnancy were embryofetotoxic and teratogenic [31]. In the rabbit, doses of 200–500 mg/kg were without harmful effects [30].

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Sulphadimethoxine

Madribon, 2,4-dimethoxy-6-sulphanilamido-1,3-diazine (MW 310.23)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care immediately before birth.

Sulphadimethoxine is a long-acting sulphonamide, used to treat staphylococcal and pneumococcal infections, as well as *Shigella* and *Salmonella*. For further information, see sulphanilamide (page 367).

Sulphadimethoxine crosses the placental barrier [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28, 29, 30, 31, 34]. There have been sporadic reports in the literature of teratogenic effects linked to the administration of long-acting sulphonamides in pregnancy, but retrospective studies [14, 15, 16] confirm that sulphadimethoxine is not contra-indicated [3, 4, 9, 12, 13, 21, 22, 28]. The drug should, however, be used with care immediately before birth, to avoid the danger of possible neonatal jaundice, particularly in premature infants [2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 17, 18, 19, 20, 21, 23, 24, 28, 31, 32, 33].

Sulphadimethoxine passes into breast milk [35].

In the mouse and rat, sulphadimethoxine was teratogenic [25], as were other sulphonamides [13, 22, 26, 27]. In the rat, oral doses of 100–300 mg/kg from the 9th to the 14th day of pregnancy caused cleft palate and malformations of the urogenital tract [25]. In the mouse, oral doses of 500 mg/kg from the 7th to the 12th day were teratogenic [25].

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Sulphadimidine

Streptotriad, Sulphamezathine,

2-(*p*-aminobenzenesulphonylamido)-4,6-dimethylpyrimidine (MW 278.32)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before birth.

Sulphadimidine is active against pyogenic cocci, pneumococci, meningococci, and coliform bacilli. For further information, see sulphanilamide (page 367).

Like all sulphonamides, sulphadimidine crosses the placental barrier [1,2,3,

4,5,6,7,8,9,10,11,12,13]. Although there are sporadic references in the literature to cases of teratogenicity related to the use of long-acting sulphonamides in pregnancy [14,15,16], sulphadimidine is not contra-indicated, because it is rapidly eliminated and does not accumulate in the foetus [3,11,17,18]. Some authors, however, maintain that sulphadimidine should be used with care immediately before birth to avoid the danger of possible neonatal jaundice, since cases have been reported following the use of rapidly eliminated sulphonamides in the last trimester [19,20].

Sulphadimidine passes into breast milk [21].

No experimental studies have been carried out on the use of sulphadimidine in pregnancy in laboratory animals.

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Sulphamethoxydiazine

(2-*p*-aminobenzene-sulphonamido)-5-methoxypyrimidine (MW 280.32)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy. but should be used with care immediately before birth.

Sulphamethoxydiazine is a methoxypyrimidine sulphonamide, and is slowly eliminated. For further information, see sulphanilamide (page 367).

Sulphamethoxydiazine rapidly crosses the placental barrier [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28]. Although there have been sporadic references in the literature to teratogenic effects related to the administration of long-acting sulphonamides in pregnancy on the basis of retrospective studies [14, 15, 16], sulphamethoxydiazine is not contra-indicated [3, 4, 9, 12, 13, 21, 22, 28, 34]. The drug should be used with care, however, immediately before birth to avoid danger of neonatal jaundice, particularly in the premature infant [2, 3, 4, 6, 7, 8, 9, 12, 13, 17, 18, 19, 20, 21, 23, 24, 28, 29, 30, 31, 32, 33, 35].

In laboratory animals, sulphamethoxydiazine, like all long-acting sulphonamides, was embryofetotoxic and teratogenic [13, 22, 25, 26, 27, 29, 30].

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Sulphadoxin

N'-(5, 6-dimethoxy-4-pyrimidine)-sulphanilamide (MW 310.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before birth.

Sulphadoxin is long-acting, and has a wide spectrum of activity (Gram-positive and Gram-negative organisms, some streptomycetes and fungi). For further information, see sulphanilamide (page 367).

Sulphadoxin rapidly crosses the placental barrier [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28]. Although there have been occasional references in the literature to teratogenic effects related to the administration of long-acting sulphonamides in pregnancy on the basis of retrospective studies [14, 15, 16], sulphadoxin is not contra-indicated [3, 4, 9, 12, 13, 21, 22, 28]. The drug should be used with care, however, close to parturition, to avoid the danger of possible neonatal jaundice, particularly in the premature infant [2, 3, 4, 6, 7, 8, 9, 12, 13, 17, 18, 19, 20, 21, 23, 24, 28].

In laboratory animals, sulphadoxin, like all long-acting sulphonamides, was embryofetotoxic and teratogenic [13, 22, 25, 26, 27].

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Sulphamoxole

2-(*p*-aminobenzenesulphamido)-4,5-dimethyl-oxazole (MW 267.31)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before birth.

Sulphamoxole has a prolonged duration of action. For further information, see sulphanilamide (page 367).

Sulphamoxole rapidly crosses the placental barrier [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28]. Although there have been sporadic references in the literature to teratogenic effects related to the administration of long-acting sulphonamides in pregnancy on the basis of retrospective studies [14, 15, 16], sulphamoxole is not contra-indicated in pregnancy [3, 4, 9, 12, 13, 21, 22, 28, 29]. The drug should, however, be used with care just before birth, to avoid the possible danger of neonatal jaundice, particularly in the premature infant [2, 3, 4, 6, 7, 8, 9, 12, 13, 17, 18, 19, 20, 21, 23, 24, 28].

In laboratory animals, sulphamoxole, like all long-acting sulphonamides, was embryofetotoxic and teratogenic [13, 22, 25, 26, 27].

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Sulphaphenazole

2-phenyl-3-sulphanilamidopyrazole (MW 314.35)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care before birth.

Sulphaphenazole is a long-acting sulphonamide. For further information, see sulphanilamide (page 367).

Sulphaphenazole rapidly crosses the placental barrier [1,2,3,4,5,6,7,8,9,10,11,12,13,28]. Although there have been sporadic references to teratogenic effects related to the use of long-acting sulphonamides in pregnancy based on retrospective studies [14,15,16], sulphaphenazole is not contra-indicated [3,4,9,12,13,21,22,28]. The drug should, however, be used with care close to birth, to avoid the danger of possible neonatal jaundice, particularly in premature infants [2,3,4,6,7,8,9,12,13,17,18,19,20,21,23,24,28].

In laboratory animals, sulphaphenazole, like all long-acting sulphonamides, was embryofetotoxic and teratogenic [13,22,25,26,27].

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Sulfaperine

2-sulphanilamido-5-methylpyrimidine (MW 264.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care close to birth.

Sulfaperine is a pyrimidine sulphonamide, with a long duration of action. For further information, see sulphanilamide (page 367).

Sulfaperine crosses the placental barrier [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28]. Although there have been sporadic references in the literature to teratogenic effects related to the use of long-acting sulphonamides in pregnancy on the basis of retrospective studies [14, 15, 16], sulfaperine is not contra-indicated [3, 4, 9, 12, 13, 21, 22, 28]. The drug should, however, be used with care immediately before birth, to avoid the danger of possible neonatal jaundice, particularly in premature infants [2, 3, 4, 6, 7, 8, 9, 12, 13, 17, 18, 19, 20, 21, 23, 24, 28].

In laboratory animals, sulfaperine, like all long-acting sulphonamides, was embryofoetotoxic and teratogenic [13, 22, 25, 26, 27].

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2.3 Sulphonamides with slight intestinal absorption

Phthalylsulphathiazole

Thalazole,

2-($-(o\text{-carboxybenzamido})\text{-benzenesulphonamide})\text{thiazole}$ (MW 403.4)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

Not contra-indicated in pregnancy, but should be used with care close to birth.

Phthalylsulphathiazole is only slightly absorbed, although it is water-soluble, and is split and activated by intestinal flora. Its action is mainly, but

not exclusively, in the intestine. Sterilization of intestinal flora, which is induced by this drug, reduces formation of vitamin K which is necessary for the hepatic biosynthesis of prothrombin. For information on the systemic effects of phthylsulphathiazole, see sulphanilamide (page 367).

Although no reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, care is advisable in the use of phthylsulphathiazole, close to birth because it may, rarely, cause neonatal jaundice [1].

No experimental studies have been described on the use of phthylsulphathiazole in pregnancy in laboratory animals.

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Sulphaguanidine

Guanimycin, *p*-aminobenzenesulphoguanidine (MW 214.24)

Not contra-indicated in pregnancy.

Sulphaguanidine is slightly absorbed from the digestive tract, and is activated by hydrolysis induced by intestinal flora.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

No experimental studies have been described on the use of sulphaguanidine in pregnancy in laboratory animals.

Salazosulphapyridine

5-(*p*-(2-pyridylsulphamoyl)phenylazo)salicylic acid (MW 398.39)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic		P	P		

To be used with care in pregnancy.

Salazosulphapyridine is a compound of salicylic acid and sulphapyridine, which is not absorbed from the gastrointestinal tract. Because of its characteristics, associated with a marked affinity for connective tissue, the drug is used in the therapy of ulcerative colitis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. Some authors [1] believe that salazosulphapyridine is not contra-indicated, while others think that it should be used with care [2, 3] (see salicylates, page 201 and sulphonamides, page 366). It is advisable to reduce the dosage to a minimum during lactation [1].

No experimental studies have been described on the use of salazosulphapyridine in pregnancy in laboratory animals.

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2.4 Sulphonamides in association

Sulphamethoxazole

3-*p*-aminobenzenesulphonamido-5-methylisoxazole (MW 253.3)

Trimethoprim

Bactrim (MW 290.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute			P	P	
Chronic			P		

This combination is not contra-indicated in pregnancy, but should be used with care before birth.

This association of a sulphonamide with an antimalarial drug permits the blocking of two consecutive metabolic steps in bacterial growth, resulting in a notable chemotherapeutic action. The sulphonamide blocks the utilization of para-aminobenzoic acid in the biosynthesis of folates. Trimethoprim, a diaminopyrimidine antimalarial, blocks the reduction of folates and thus the biosynthesis of purines and pyrimidines. The combination is harmless to human cells, which do not synthesize folates and which have a different folate reductase which is less sensitive to trimethoprim. However, it is better not to administer this drug to patients with haematological disorders or folate deficiency. Trimethoprim/sulphamethoxazole is used in the treatment of respiratory, urinary, and genital infections.

Trimethoprim/sulphamethoxazole crosses the placental barrier [4]. It is not contra-indicated in pregnancy [1, 2, 5, 6, 7], although it is preferable not to use this combination immediately before parturition because of the danger of neonatal jaundice [5, 6, 7]. No embryofoetotoxic or teratogenic effects have been reported [1] in an investigation on 120 patients treated with the drug at various stages of pregnancy, including the period of organogenesis. A healthy infant was born to a patient who had taken trimethoprim/sulphamethoxazole throughout pregnancy [2].

In the rat, trimethoprim/sulphamethoxazole sometimes caused teratogenic effects [3]. Oral doses of 200–2000 mg/kg from the 8th to the 16th day of pregnancy were foetotoxic and teratogenic [3].

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3. CHEMOTHERAPY FOR URINARY TRACT INFECTIONS

Some chemotherapeutic drugs reach therapeutically effective concentrations in the renal parenchyma and in the urine. After mephenamine, numerous drugs were synthesized which had a nitrofurane structure (nitrofurantoin, hydroxymethylnitrofurantoin, nifurpipone) or a quinolone structure (nitroxoline, oxilinic acid). Nalidixic acid and phenazopyridine were also produced. The following drugs are discussed in this chapter:

	Recommendation	Page
Methenamine	NC	387
Nitrofurantoin	P	388
Hydroxymethylnitrofurantoin	P	389
Nifurpipone	P	390
Nitroxolin	P	391
Oxolinic acid	P	391
Nalidixic acid	NC	392
Pyromidic acid	NC	393
Phenazopyridine	NC	394

Methenamine is not contra-indicated in pregnancy. The nitrofuranes are not contra-indicated, but should be used with care in the last part of pregnancy because of possible haemolytic effects in the neonate. Limited experience with quinoline drugs suggests that they be used with care in pregnancy. Nalidixic acid and phenazopyridine are not contra-indicated.

Methenamine

Hiprex, hexamethylenetetramine (MW 140.19)

Not contra-indicated in pregnancy.

Methenamine is formed by the condensation of formaldehyde and ammonia, and is a urinary and intestinal tract antiseptic which acts by releasing formaldehyde in an acid environment. Of the amount ingested, 10–30% is degraded in the stomach, and the rest is eliminated in the urine. Its therapeutic action depends upon the acidity of the urine.

Methenamine has been used throughout pregnancy [1], or during the third trimester [2], without harmful effects on the foetus or the mother. It should be borne in mind that during therapy with this drug, there may be reduced levels of oestriol, since formaldehyde can destroy plasma oestriol [2, 5].

In the rat and rabbit, methenamine was neither foetotoxic nor teratogenic [3,4] at therapeutic doses. In the rat, doses of 800 mg/kg were harmless [4]. In the rabbit, doses of 100 mg/kg were without harmful effects, while 800 mg/kg doses (20 times therapeutic) were highly toxic both to the mother and the foetus, causing intra-uterine death [4].

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Nitrofurantoin

Berkfurin, Ceduran, Furadantin, Macrochantin,
N-(5-nitro-2-furfurylidene)-1-aminohydantoin (MW 238.16)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in late pregnancy.

Nitrofurantoin, a derivative of furane, is a chemotherapeutic drug active against both Gram-positive and Gram-negative bacteria. It is used exclusively as a urinary antiseptic. It is rapidly absorbed from the gastrointestinal tract and excreted in the urine, where it readily reaches therapeutic levels. Nitrofurantoin can induce haemolytic anaemia when there is a congenital deficiency in glucose-6-phosphate dehydrogenase in erythrocytes. Other side effects include leucopenia, cholestatic jaundice, and liver cell damage.

Nitrofurantoin crosses the placental barrier [7,15]. It has been used in pregnancy without side effects in the mother or the foetus [1,2,14,16], and our own clinical experience is similar. In 56 patients with asymptomatic urobacilli, nitrofurantoin at a dose of 200 mg/kg throughout pregnancy caused no harmful effects in the foetus [1]. In 101 patients with the same symptomatology, doses of 200–400 mg/kg throughout pregnancy did not cause malformations or toxic effects [2]. Cases of haemolytic anaemia and neonatal jaundice linked to the use of nitrofurantoin have, however, been reported. These symptoms, which are analogous to those occurring in the adult, are exacerbated by congenital deficiency of glucose-6-phosphate dehydrogenase [4,5,6,8,9,10,11,12,13,16,17,18,21].

Nitrofurantoin passes into breast milk [19,20].

In the dog, guinea-pig, sheep, and rabbit, transplacental passage and foetal metabolism of nitrofurantoin have been established, but there were no harmful effects linked to its administration in pregnancy [7].

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Hydroxymethylnitrofurantoin

N-(5-nitro-2-furfurylidene)-1-amino-hydroxymethyl-hydantoin (MW 268.19)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be use with care in late pregnancy.

Hydroxymethylnitrofurantoin is a nitrofurane which, compared to nitrofurantoin, has greater urinary elimination and thus, at the same doses, greater therapeutic efficacy. Its antibacterial activity is similar to that of nitrofurantoin (see page 388).

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3,6]. Hydroxymethylnitrofurantoin should, however, be used with care in late pregnancy for similar reasons to nitrofurantoin (see page 388). Administration of hydroxymethylnitrofurantoin at doses of 160 mg/day orally to 30 patients with cystopyelitis at various stages of pregnancy for a maximum period of 8 days was without harmful effects [6].

In the mouse, rat, and rabbit, hydroxymethylfurantoin was neither embryofetotoxic nor teratogenic [4,5]. In the mouse, oral doses of 10–20–50–100–160 mg/kg at various stages of gestation were innocuous, and similar results were observed in the rat, with doses of 10–50–90 mg/kg, and in the rabbit, with doses of 10–50 mg/kg [4,5].

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Nifurpipone

4-methyl-piperazino-acethydrazone of 5-nitrofurfurol (MW 313.32)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in late pregnancy.

Nifurpipone is a synthetic nitrofurane, with a similar spectrum of activity to that of nitrofurantoin, differing only in being more water soluble. It is used as a urinary antiseptic.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, nifurpipone should be used with care in late pregnancy for the same reasons as given for nitrofurantoin (see page 388).

In the rat and rabbit, nifurpipone was neither embryofetotoxic nor teratogenic [1,2,3]. In the rat, oral doses of 20–60 mg/kg from the 2nd to the 15th day of pregnancy did not cause malformations or intra-uterine death, nor was the number of live births reduced or postnatal development affected [1]. In the rabbit, oral doses of 10–100–200 mg/kg from the 6th to the 18th day of pregnancy were not teratogenic. Only at doses of 200 mg/kg was nifurpipone toxic to the pregnant animals, with harmful effects on the foetus [2]. In the rat and rabbit, doses of up to 50 mg/kg were not teratogenic [3].

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Nitroxolin

5-nitro-8-hydroxyquinoline (MW 190.15)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Nitroxolin, a quinoline derivative, is a chemotherapeutic agent with a wide spectrum of activity. It acts against both Gram-positive and Gram-negative organisms (*Staphylococcus aureus*, *Salmonella paratyphi*, *Pseudomonas aeruginosa*, etc.), on mycobacteria (Koch bacillus), and on some fungi (*Candida albicans*). Its action on *Proteus*, however, is less effective. Administered orally, it is rapidly absorbed and reaches maximal concentrations in the urinary tract within 4 hours.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 4]. However, we maintain that nitroxolin should be used with care in pregnancy because of insufficient clinical information. In three cases of pyelonephritis in the second trimester, oral treatment with 400 mg/day nitroxolin for 5–10 days was without harmful effects [4].

In the rat, nitroxolin was not teratogenic [3]. Oral doses of 25–50–100–200 mg/kg (5–40 times therapeutic) throughout pregnancy were innocuous [3].

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Oxolinic acid

5-ethyl-5, 8-dihydro-8-keto-1, 3-dioxolo-quinoline-7-carboxylic acid (MW 261.2).

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Oxolinic acid is a synthetic chemotherapeutic agent with a quinoline structure, and bactericidal action, principally against Gram-negative organisms (in particular *Proteus*), although it is effective against some Gram-positive

bacteria. Oxolinic acid also has a slight stimulant action on the central nervous system. The mechanism of action of oxolinic acid depends on inhibition of the biosynthesis of DNA in sensitive organisms. A cross-resistance with nalidixic acid has been shown. On oral administration, oxolinic acid is rapidly absorbed and almost totally excreted in the urine. Therapeutically effective blood and urinary concentrations are reached during the first hour. Oxolinic acid is used exclusively in the treatment of urinary tract infections. It is contra-indicated in epilepsy.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. Some authors [1,2,3] advise care in the use of oxolinic acid in pregnancy, since its safety has not yet been sufficiently demonstrated.

In the rat, mouse, and rabbit, oxolinic acid was neither embryofetotoxic nor teratogenic [1,4,5,6,7,8,9,10,11]. Oral doses of 10–100 mg/kg were not teratogenic, did not affect birth, the number of live neonates, or lactation [4,7,9]. At a dose of 200 mg/kg, from the 6th to the 18th day of pregnancy, the drug increased neonatal mortality [5,6,8,10]. In the rat, oxolinic acid passed into the milk, but in amounts too low to be toxic to the sucklings [9]. In the rabbit, oral doses of 100–300 mg/kg from the 6th to the 16th day of pregnancy were not teratogenic [11].

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Nalidixic acid

Negram,

1-ethyl-7-methyl-1,8-naphthiridin-4-one-3-carboxylic acid (MW 232.23)

Not contra-indicated in pregnancy.

Nalidixic acid, a derivative of naphthiridine, is excreted principally in the urine, and is used in acute and chronic infections of the urinary tract involving

Escherichia, *Proteus*, *Aerobacter*, and *Klebsiella*. Its action is independent of urinary pH.

Nalidixic acid does not cross the placental barrier [14], but it does pass into maternal milk in small amounts [15]. It has been used at various stages of pregnancy with no side effects in the mother or the foetus [6,7,11,13,14,16]. Some authors advise against the use of nalidixic acid in the perinatal period, because it is metabolized to only a small extent in the neonatal liver [1], and can cause hypermolytosis [16]. Others advise against its use in the first trimester as a simple precaution [2,3,4,5,17]. One patient was treated with doses of 4 g and then of 2 g/day during the first trimester. Her coliform infection regressed satisfactorily with no harmful effects on the foetus [6]. Four patients in the second trimester were treated with nalidixic acid, and produced normal infants [7].

In the rat, monkey, and rabbit, nalidixic acid was not teratogenic [10,12]. Only at very high doses was it foetotoxic in the rat [8]. Oral doses of 75–150 mg/kg throughout pregnancy were neither embryofoetotoxic nor teratogenic in the rat, but a dose of 300 mg/kg caused abortions and was lethal to the pregnant animal [8]. In the monkey, a dose of 200 mg/kg 8 weeks before birth had no harmful effects on the foetus [8].

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Piromidic acid

5,8-dihydro-8-ethyl-5-oxo-2-pyrrolidino-pyrido(2,3-*d*)-pyrimidino-6-carboxylic acid (MW 288.9)

Not contra-indicated in pregnancy.

Piromidic acid is a synthetic drug which is active principally against Gram-negative organisms (its spectrum of activity is similar to that of nalidixic acid). Its mechanism of action is linked to the peripheral conversion of piromidic acid to beta-hydroxypiromidic acid. It is used mainly in the treatment of urinary, intestinal, and biliary infections.

The transplacental passage of piromidic acid has been demonstrated. Oral doses of 1 g given to 16 pregnant women gave levels in the foetus and in cord blood which were lower than maternal blood concentrations after 2 hours [1]. No embryofoetotoxic or teratogenic effects have been observed [1,2]. Administered to 5 patients in the second half of pregnancy, at a dose of 1–2 g/day orally, piromidic acid had no harmful effects on the foetus [1]. Administered to one patient in the first 2 months of pregnancy at a total dose of 45 g, the drug had no foetal side effects [2].

Piromidic acid passes into breast milk [1]. After administration of 1 g to the mother, the drug was found in the milk at a concentration of 1.2–2.5 $\mu\text{g/ml}$, equal to 15–45% of maternal serum levels [1].

No experimental studies on the use of piromidic acid in pregnancy in laboratory animals have been described.

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Phenazopyridine

Uromide, 3-phenylazo-2,6-diaminopyridine (MW 113.23)

Not contra-indicated in pregnancy.

Phenazopyridine is a urinary tract antiseptic with additional analgesic activity. It is administered orally, and is rapidly absorbed from the gastrointestinal tract, and equally rapidly eliminated via the kidneys, usually within 20 hours of administration. Phenazopyridine may be precipitated in the urine (urinary calculus) and may cause methaemoglobinaemia.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1,2,3,4,5]. In 35 patients, administration of phenazopyridine at a dose of 900 mg/day from the 16th to the 37th week of pregnancy had no harmful effects on the foetus [4]. In 3 patients, respectively in the 4th, 5th, and 7th months of pregnancy, administration of the drug at doses of 1.2 g/day for a maximum of 7 days was neither embryofoetotoxic nor teratogenic [5].

In the rat and rabbit, phenazopyridine was neither embryofoetotoxic nor teratogenic [6]. In the rat, oral doses of 50–250 mg/kg from the 6th to the 15th day of pregnancy, and in the rabbit, doses of 100 mg/kg from the 6th to the 18th day of pregnancy, were innocuous [6].

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4. ANTITUBERCULOUS CHEMOTHERAPY

In addition to some antibiotics (streptomycin, cycloserine, viomycin, kanamycin, rifamicin) there are specific drugs available for the treatment of tubercular infections, including para-aminosalicylic acid and isoniazid as first line drugs, and ethambutol, pyrazinamide, thiocarlide, morinamide, and terizidone for second line use. The latter group are more liable to produce bacterial resistance, but this may be reduced by using a combination of drugs to start with. The following drugs are discussed in this chapter:

	Recommendation	Page
Para-aminosalicylic acid	NC (C during lactation)	396
Ethambutol	NC	397
Isoniazid	P	400
Metamiazide	P	401
Pashydrazide	P	402
Pyrazinamide	NC	402
Thiocarlide	NC	403
Morinamide hydrochloride	NC	403
Terizidone	NC	404

Isoniazid should be used with care in pregnancy because of its toxic effects on the foetus; a teratogenic action cannot be excluded. All the other drugs are not contra-indicated, even though there may be only limited information available on their use. However, we believe that there are insufficient data in the literature on the following drugs to make a recommendation as to their use in pregnancy: hydrazide of cyanacetic acid, pasiniazide, furonazide, gluconiazide, sulphoniazide, verazide (see pages 404–405).

Para-aminosalicylic acid or PAS

(MW 153.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic					C

Not contra-indicated in pregnancy, but is contra-indicated during lactation.

PAS is a tuberculostatic drug which is less efficacious in the exudative

forms of the disease, and is used almost exclusively in association with streptomycin or isoniazid. PAS has the same therapeutic actions as the salicylates, but its mechanism of action is not known. It could act in an analogous manner to the sulphonamides, as an antimetabolite of para-aminobenzoic acid.

PAS crosses the placental barrier [10,13]. No teratogenic effects related to its use at any stage of pregnancy have been reported [2,3,4,5,6,7,8,9,11,12,14,16,18]. However, there may be signs of intolerance, especially during the second trimester [2].

It is preferable not to use PAS during lactation, because it passes into breast milk [17] and may cause gastrointestinal disturbances in the infant [2].

In the rat and rabbit, PAS was neither embryofoetotoxic nor teratogenic [15]. In the rat, oral doses of 3.85–385 mg/kg from the 6th to the 14th day of pregnancy were harmless [15]. In the rabbit, oral doses of 5 mg/kg from the 7th to the 14th day of pregnancy had no side effects [15].

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Ethambutol dihydrochloride

Miambutol,

(D), 2'-(ethylenediimino)-di-1-butanol dihydrochloride (MW 277.2)

Not contra-indicated in pregnancy.

Ethambutol is a synthetic chemotherapeutic drug, active orally, which interferes with the synthesis of metabolites necessary for the multiplication of the mycobacteria. The detailed mechanism of action, is, however, not known.

The most serious side effect of ethambutol is optic neuritis which leads to a

diminution in the perception of green colours. In addition, ethambutol is able to increase uricaemia in some patients.

Ethambutol has been administered at various periods of pregnancy without damage to the mother or the foetus [1, 2, 3, 4, 5, 6, 7, 8, 9, 20, 21, 22, 23, 24, 25, 30, 31, 32].

Reference is made in the literature to many cases in which the drug, when administered throughout the pregnancy, was not teratogenic [1, 2, 3, 4, 5, 20, 21]. In other investigations ethambutol was used in the first half of pregnancy without the presence of any notable embryofoetotoxic or teratogenic effects [6, 7].

The drug was administered at doses of 15–25 mg/kg, in 42 patients: for the whole period of pregnancy (57% of cases), in the first trimester (66%), and in the third trimester (76%); in 8 neonates minor malformations were noted, which, however, were not necessarily related to the use of the drug [8].

In 6 embryos obtained at therapeutic abortion in patients who had taken the drug before and during pregnancy, no macroscopic or microscopic anomalies were noted [9].

A retrospective study of 182 pregnant women treated with ethambutol and/or rifampicin did not show any embryofoetotoxic effects attributable to either drug [28].

In the mouse, rat, and rabbit, conflicting results have been obtained regarding teratogenicity [10, 11, 12, 14, 15, 16, 17, 18, 19, 26, 30]. In the experience of many authors (referred to below in detail) ethambutol was embryofoetotoxic and teratogenic only at higher doses than those used in therapy. However, at doses commonly used in humans, the drug was considered to be harmless to the foetus, in analogy to experiments on laboratory animals.

In the mouse, oral doses of 250–2500 mg/kg from the 7th to the 12th day of pregnancy gave rise to only one case of retarded ossification of the phalanges and the caudal vertebrae [10]. Oral doses of 7.5 mg/day from the 6th to the 13th day of pregnancy were teratogenic [11]. Oral doses of 50–200 mg/kg from the 6th to the 14th day of pregnancy were embryofoetotoxic and teratogenic [12, 29]. Doses of 25–160 mg/kg, before and throughout pregnancy, were embryofoetotoxic and reduced fertility [14].

In the rat, ethambutol added to the diet at a concentration of 0.2–0.8% before and throughout pregnancy was innocuous [15]. A dose of 120–200 mg/kg from the 6th to the 16th day of pregnancy was teratogenic, and at the maximum dose, lethal [16]. Oral doses of 200 mg/kg from the 6th to the 14th day of pregnancy caused malformations of the digestive tract and cleft palate [17, 29]. Oral doses of 270 mg/kg from the 6th to the 14th day of pregnancy had dubious teratogenic effects [17].

In the rabbit, oral doses of 100–250–500 mg/kg from the 8th to the 16th day of pregnancy were not teratogenic. Only at doses of 250 mg/kg was ethambutol foetotoxic, causing an increase in foetal mortality [18]. Doses of

13.5–27 mg/kg orally from the 7th to the 14th day of pregnancy were neither embryofetotoxic nor teratogenic [19].

Other authors [26] exclude the possibility that ethambutol has an elective toxicity for the foetus. In rats and rabbits treated subcutaneously at doses of 10–70 mg/kg there was no significant foetotoxic action, while at higher doses, there was an increased incidence of foetal resorption. Even although these experiments were conducted with very high doses, and notwithstanding the fact that in humans, treatment of patients at various stages of pregnancy with ethambutol did not adversely affect the pregnancy or the infant [22], the producers of the drug advise care in its use in pregnancy. Considering the advantages offered by ethambutol in the treatment of tuberculosis, and its wide clinical use, we do not consider that the drug is contra-indicated in pregnancy.

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Isoniazid

Rimifon, Rifinah, Rimactazid, Mynah, Inapasade,
isonicotinic acid hydrazide (MW 137.15)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Isoniazid has bacteriostatic and bacteriocidal actions on tubercular mycobacteria. Its mechanism of action is still uncertain, although it probably interferes with the biosynthesis of some constituents of bacterial cells (lipids, nucleic acids) and with energy metabolism. It rapidly diffuses into all cells and biological fluids. The principal side effects of isoniazid are its central and peripheral neurotoxicity and hepatotoxicity.

Isoniazid crosses the placental barrier [1,2,3,4,5,24]. Data on its effects in pregnancy are contradictory. While some authors [6,7,8,9,10,12,23,25,26,27,31] maintain that isoniazid is completely innocuous when administered at various stages of pregnancy, others [5,13,14,28,29] believe that it is possible after prolonged treatment to produce neurotoxic effects in the foetus. Still others think that isoniazid may be teratogenic [4,16]. Administration of isoniazid prophylactically at an oral dose of 6 mg/kg/day to 87 patients from the 7th to the 8th month of pregnancy was not foetotoxic [7]. Of 118 patients treated with isoniazid at various stages of pregnancy, 5 had malformed fetuses [16], although the statistical significance of this was not evaluated.

Isoniazid passes into breast milk [30].

In the rat, mouse, and rabbit, transplacental passage of isoniazid was demonstrated [17,18,22]. Data on possible embryofoetotoxic or teratogenic effects, however, were not consistent [18,19,20,21]. In the rat, oral administration of 0.1–15.9 mg/kg from the 6th to the 14th day of pregnancy did not cause embryofoetotoxic effects, and malformations observed could not be attributed with certainty to isoniazid [19].

In the mouse, a subcutaneous dose of 5 mg/kg/day from the 6th to the 13th day of pregnancy caused an increase in foetal resorptions and teratogenic effects, including malformations of the limbs and polydactyly [20]. Administration of 100–300 mg/kg from the 7th to the 12th day of pregnancy caused a slight increase in foetal resorptions, but no malformations [21].

In the rabbit, oral doses of 30–120 mg/kg from the 5th to the 27th day of pregnancy, and oral doses of 1.5–5 mg/kg from the 7th to the 14th day of pregnancy were innocuous [18,19].

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Metanizide

isonicotinic hydrazide calcium methanesulphonate (MW 231.24)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Metanizide is a derivative of isoniazid, but differs from the latter in having equal mycobacterial activity with five times less toxicity. For these reasons, it is much better tolerated during prolonged treatment. Side effects on the liver, digestive tract, nervous system, and skin have not been observed.

The methanesulphonate derivative does not form intermediate compounds (hydrazones) which could increase its toxicity. It is particularly useful in the localization of meningitis, in that it concentrates in cerebrospinal fluid, and the urogenital tract, thus giving preferential displacement of active metabolites in the urinary tract.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, because of the similarity between metanizide and isoniazid, care is advised in its use.

In the rat and rabbit, metanizide was not teratogenic, and did not affect fertility [1]. Administration of the drug to male and female rats prior to mating did not affect the resulting pregnancy [1]. In the rabbit, oral doses of 35 mg/kg from the 6th to the 16th day of pregnancy were not teratogenic [1].

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Pashydrazide

para-aminosalicylic acid hydrazide (MW 167.16)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Pashydrazide is the hydrazide of para-aminosalicylic acid.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1]. However, because of the similarity between pashydrazide and isoniazid, the former should be used with care in pregnancy.

No experimental studies have been described on the use of pashydrazide in pregnancy in laboratory animals.

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Pyrazinamide

Zinamide, pyrazine-carbonic acid amide (MW 123.11)

Not contra-indicated in pregnancy.

Pyrazinamide has a similar structure to isoniazid, and a tuberculostatic activity which lies between that of para-aminosalicylic acid and streptomycin. Pyrazinamide is used only in association with other antitubercular drugs, for example isoniazid, since resistance to it develops rapidly.

Transplacental passage of pyrazinamide has been shown [1], but its use in pregnancy is not contra-indicated [2,3]. No embryofoetotoxic or teratogenic effects have been observed [4].

No experimental studies have been described on the use of pyrazinamide in laboratory animals, and the manufacturers were unable to provide any data [5].

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Thiocarlide

4,4'-di-isoamyloxy-thiocarbanilide (MW 400.6)

Not contra-indicated in pregnancy.

Thiocarlide is usually used in combination with other antitubercular drugs, the action of which it potentiates.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy.

In the rat, oral doses of 4 g/kg/day at various stages of pregnancy caused no embryofoetotoxic or teratogenic effects [1].

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Morinamide hydrochloride

N-(morpholinomethyl)pyrazinamide hydrochloride (MW 258.7)

Not contra-indicated in pregnancy.

Morinamide is a recently synthesized drug which has been used in pulmonary and extrapulmonary forms of tuberculosis which were resistant to other therapy.

Clinical experience of the use of morinamide in pregnancy is rare. Some cases have been reported in which the drug was used in pregnancy without harmful effects on the mother or the foetus [1,2].

In the rat, mouse, and rabbit, morinamide was neither embryofoetotoxic nor teratogenic. In the rat, oral doses of 100–500 mg/kg from the 6th to the 17th day of pregnancy were harmless to the foetus [3]. Oral doses of 150–300 mg/kg throughout pregnancy did not cause significantly more malformations than in a control group [4]. In the mouse, oral doses of 250 mg/kg

throughout pregnancy were not teratogenic [4, 5], while doses of 100–500 mg/kg for the same period caused an increase in foetal resorptions and abortions, with some malformations [6].

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Terizidone

1,4-bis-D-(3-oxo-4-isoxazolidinyl-iminomethyl)benzene (MW 306.32)

Not contra-indicated in pregnancy.

Terizidone is an antitubercular drug whose bacteriostatic action is potentiated by association with other such drugs.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [3, 4, 5, 6, 7].

In the rat and rabbit, no embryofoetotoxic or teratogenic effects were observed [1, 2]. In the rat, oral doses of 50–300 mg/kg from the 6th to the 15th day of pregnancy (therapeutic dose 1 g/day) were innocuous [1]. In the rabbit, oral doses of 100 mg/kg from the 6th to the 18th day of pregnancy were harmless. In one case, a slight effect was noted on the pregnant animal, with anorexia and loss of weight [2].

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* * * * *

Cyanacetic acid hydrazide or cyanacethydrazide

(MW 99.09)

Pasiniazide

isonicotinic acid hydrazide para-aminosalicylate (MW 290.27)

Pasiniazide is an equimolecular combination of isonicotinic acid hydrazide and para-aminosalicylic acid.

Furonazide

isonicotinylhydrazone of phenyl-2-methyl ketone (MW 239.27)

Furonazide is a chemotherapeutic drug active in all pulmonary and extra-pulmonary infections caused by mycobacterium *Tuberculosis*, with a mechanism of action which is not clearly understood. It reduced the activity of dicoumarol and diphenylhydantoin. Its catabolism is slowed by salicylates, while association with rifampicin potentiates its hepatotoxicity. Furonazide can cause hypersensitivity.

Gluconiazide

isonicotinylhydrazone of glucuronolactone (MW 295.25)

Sulphoniazide

isonicotinylhydrazone of *m*-sulphon-benzaldehyde sodiun salt (MW 327.27)

Verazide

1-isonicotinoyl-2-veratrylidene hydrazide (MW 269.25)

We have been unable to obtain any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. Although no harmful effects have been reported, we believe that in the absence of sufficient evidence of their safety, they should be contra-indicated in pregnancy and in women of childbearing age who are likely to conceive.

5. ANTIFUNGAL CHEMOTHERAPY

Numerous mycotic infections are usually treated by local application of drugs which have no systemic action. Some antifungal drugs are used orally (nystatin, clotrimazole) or parenterally (amphotericin B), and only in these cases is it necessary to consider possible effects on the foetus. The following drugs are described in this chapter:

	Recommendation	Page
Nystatin	NC	406
Amphotericin B	NC (topical)	407
	C (parenteral)	407
Griseofulvin	C	408
Clotrimazole	NC (topical)	409
	C (oral)	

Nystatin is not usually contra-indicated during pregnancy, and is not absorbed from the digestive tract. Griseofulvin is contra-indicated because it crosses the placental barrier and has shown antimitotic activity. Amphotericin B and clotrimazole are contra-indicated by parenteral routes.

Nystatin

Nystan, Trimovate, Nystavescent, Timodine (MW 948.1)

Not contra-indicated in pregnancy.

Nystatin is a natural antibiotic with a similar structure to that of amphotericin B. It is produced by *Streptomyces noursei*. Nystatin has not yet been synthesized, and its activity is expressed in units. It has fungistatic and fungicidal actions because it attaches in a stable manner to the cell membrane of sensitive strains, altering their permeability. Nystatin is used in the treatment of *Candida*. Absorption of nystatin across the walls of the digestive tract or mucosa is negligible, and therefore the drug is quite harmless to the foetus in pregnancy.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 4, 5, 6, 7, 8], although some authors believe that nystatin should be used with care, particularly in the last months of pregnancy, because it can cause dental dyschromia in the neonate [3]. Fourteen pregnant women with vaginal moniliasis were treated with nystatin topically at a dose of 100 000 units/day for 15 days, with good therapeutic results and no foetal side effects [7]. Another study on 147 pregnant women with vaginal moniliasis treated

locally and orally with nystatin showed good control of infection with no effects on the foetus [8].

No experimental studies have been described on the use of nystatin in pregnancy in laboratory animals.

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Amphotericin B

Fungilin, Fungizone, Mysteclic (MW 924.06)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated parenterally but not topically in pregnancy.

Amphotericin is a natural polyene antibiotic, produced by *Streptomyces nodosus*, and has both fungistatic and fungicidal actions. Amphotericin is scarcely absorbed orally and therefore has to be administered intravenously. Its toxicity is significant. It can provoke anaemia, thrombocytopenia, hepatic insufficiency, renal, glomerular, and tubular damage, acidosis, and hypopotassaemia. It is used in disseminated fungal infection, with close monitoring of hepatic, renal, and haematopoietic function. In topical therapy, there are no significant manifestations of toxicity.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2]. We maintain, however, that on the basis of the experimental data referred to below, amphotericin is contra-indicated in pregnancy only when given intravenously. Because of its poor absorption, it can be used topically (intravaginal) without harm to the mother or the foetus. A patient who was 24 weeks pregnant was treated for an infection of *B. dermatitides* with amphotericin B at doses of 0.2–1 mg/kg intravenously for 30 days, without foetal side effects [2].

In the rat, mouse, and rabbit, amphotericin B was embryofoetotoxic but not teratogenic [1]. In the rat, oral doses of 50–200 mg/kg were embryofoetotoxic, with an increase in foetal resorption. Similar doses in the mouse were foetotoxic, with an increase in perinatal mortality, but in neither species were there

teratogenic effects [1]. In the rabbit, oral doses of 25–100 mg/kg/day were neither embryofetotoxic nor teratogenic [1].

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Griseofulvin

Fulsin, Grisovin (MW 352.77)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		

Contra-indicated in pregnancy.

Griseofulvin is an antibiotic which inhibits the growth of those fungi responsible for cutaneous mycosis, probably by interfering with the synthesis of the mycelia walls. It also damages animal cells in culture, causing inhibition of mitosis with blockage of the metaphase and irregular regrouping of chromosomes. In the rat, administration of griseofulvin for a long period can cause temporary suppression of spermatogenesis. In man, griseofulvin at a dose of 2 g/day for 3 months does not affect germinative epithelium or sperm [7, 9]. The drug can give rise to a series of actions, the significance and mechanisms of which are not completely understood, but which open the way to a large number of therapeutic applications.

Griseofulvin crosses the placental barrier, reaching foetal blood (at the end of pregnancy) in concentrations equivalent or lower than those in maternal blood. It does not pass into amniotic fluid [15]. No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1], although some authors advise care in its use in pregnancy because of insufficient clinical data [2, 3, 4]. It is believed that griseofulvin is potentially teratogenic [10, 11, 12, 13, 14].

In the rat, griseofulvin was embryofetotoxic and teratogenic at high doses [5], while at low doses it had no harmful effects on either the pregnancy or the offspring [6, 7]. In rats treated with 20–30 mg/kg (therapeutic dose 500–1000 mg/day) griseofulvin did not affect fertility or the course of pregnancy [6, 7], while at doses of 125–1500 mg/kg orally from the 6th to the 15th day of pregnancy it caused changes in bone and anal atresia [5]. The highest incidence of malformations was obtained in the offspring of animals treated with 1250–1500 mg/kg.

We believe that griseofulvin is contra-indicated in pregnancy, and should

thus be used only when absolutely necessary, because of its mechanism of action, and the results of studies on laboratory animals.

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Clotrimazole

Canesten, bis-phenyl-(2-chlorophenyl)-1-imidazolyl-methane (MW 344.8)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C				
Chronic	C	C	C		

Contra-indicated orally but not topically in pregnancy.

Clotrimazole is an antimycotic chemotherapeutic agent which is effective against Gram-positive bacteria and *Trichomonas* as well. Its exact mechanism of action is not known, but seems to be linked to inhibition of protein synthesis at the cell membrane.

Clotrimazole may be used intravaginally or topically in pregnancy, since its absorption via these routes is virtually nil, because of its low solubility [6]. It thus has no systemic effects [1,7]. It is, however, contra-indicated orally, particularly in the first trimester, because it can cause damage to the liver and adrenal glands [9]. Clotrimazole has been administered at various stages of pregnancy locally for vaginal infections without foetal toxicity, growth retardation, intra-uterine death, or malformations [1,2,3]. There have been no reports of harmful effects in the mother either [3,4,5,8,11,12,13], and our own clinical experience supports this view.

In the rat, clotrimazole was neither embryofetotoxic nor teratogenic [6,10]. Intravaginal doses of 10–30–100 mg/kg from the 6th to the 15th day of pregnancy were without harmful effects [6,10].

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6. TRICHOMONAL CHEMOTHERAPY

Metronidazole was the first of the nitro-imidazoles with trichomonocidal activity. When used in topical therapy, it is often combined with oral treatment with the aim of producing systemic effects. The following drugs are discussed in this chapter:

	Recommendation	Page
Metronidazole	NC (topical) } P (oral) }	411
Nifuratel	NC	413
Nimorazole	NC	414
Tenitrazole	NC (topical)	414
Mepartricine	NC	415
Azanidazole	NC (topical) } P (oral) }	415

None of these drugs is contra-indicated in pregnancy when applied topically. The safety of metronidazole is, however, doubtful when administered orally, especially in the first trimester.

Metronidazole

Flagyl, 1-hydroxyethyl-2-methyl-5-nitro-imidazole (MW 171.6)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P				

To be used with care orally, and is not contra-indicated topically in pregnancy.

Metronidazole is a derivative of 2-nitro-imidazole, and is specifically active against *Trichomonas vaginalis*. Its mechanism of action is not linked to an inhibition of growth, but to a direct trichomonocidal action. It also interferes with the formation of inosinic acid, a precursor of purines.

Metronidazole crosses the placental barrier [2, 3, 9, 12]. Although no embryo-foetoxic or teratogenic effects have been observed [2, 4, 5, 6, 7, 8, 10, 16, 17, 18, 29, 31, 32], and there are no side effects in the mother (except for a transitory leucopenia) [5, 11, 12, 17], some authors advise against the use of metronidazole orally because of possible accumulation in the foetus [9, 12, 13] and because of an increase incidence of malformations in the first trimester [14, 22, 23].

The case has been described of a pregnant women who had ingested 21 tablets (200 mg each) of metronidazole without experiencing any disturbances except for a slight disorientation. The foetus was unaffected [17]. Metronidazole taken in a dose of 200 mg three times a day for 7 days was prescribed for 61 patients at various stages of pregnancy. In three cases, there were intra-uterine deaths of the foetus before the end of pregnancy, and in one case the infant died as a result of asphyxia pallida. No malformations attributable to the drug were observed. The authors concluded that the drug could be prescribed with safety in the second and third trimesters, but thought that further experimental studies were necessary to prove its safety in the first trimester [18]. In a study conducted on 1469 pregnant women who had taken metronidazole at various stages of pregnancy including the first trimester, there was no evidence of an increase in malformations, abortions, or perinatal deaths [29].

Metronidazole passes into breast milk in concentrations equal to those in maternal serum. However, the effects on the infant seem to be minimal or absent, as the drug was rapidly excreted by the kidneys and did not accumulate in the tissues [2, 6, 9, 12].

In the rat, metronidazole administered throughout pregnancy was neither embryofetotoxic nor teratogenic [30]. In the mouse, oral administration caused an increased incidence of tumours [27, 28, 32]. It should be emphasized that according to some recent investigations, metronidazole and its metabolites have a mutagenic action in certain bacterial species [19, 24, 25, 26, 32, 33]. The liver microsomes of mammals can transform the drug into the hydroxyamino or amino derivatives responsible for such activity [20], which was also observed in human lymphocyte cultures following high doses for long periods [21].

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Nifuratel or methylmercadone

N-(5-nitro-2-furfurylidene)-3-amino-5-methylmercaptomethyl-2-oxazolidinone (MW 285.3)

Not contra-indicated in pregnancy.

Nifuratel is a synthetic chemotherapeutic agent active locally and systemically against Gram-positive and Gram-negative bacteria, and particularly against *Trichomonas vaginalis*. It also has antifungal properties and is used in gynaecology and virology.

The use of nifuratel in pregnancy, both topically and systemically, produced no embryofoetotoxic or teratogenic effects [1, 2, 3, 4, 5, 7, 9, 10, 11, 12]. Used at therapeutic doses orally or vaginally in 5 patients from the 10th to the 15th week of pregnancy, nifuratel caused no harmful effects [4]. It was also shown to be innocuous after administration of 400 mg orally or 250 mg vaginally for 10 days in 50 patients at various stages of pregnancy [5].

In the rat, mouse, and rabbit, nifuratel was neither embryofoetotoxic nor teratogenic [6, 7, 8]. In the rat, oral administration of a dose of 200 mg/kg from the 7th to the 17th day of pregnancy, or of 10–200 mg/kg throughout pregnancy was innocuous [6]. In the mouse, oral doses of 200 mg/kg from the 2nd to the 21st day of pregnancy were without harmful effects [6]. In the rabbit, oral doses of 100 mg/kg from the 7th to the 15th day of pregnancy were not teratogenic but did cause an increase in foetal resorption [6].

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Nimorazole

Naxogin, 1-(*N*- β -ethylmorpholino)-5-nitro-imidazole) (MW 226.23)

Not contra-indicated in pregnancy.

Nimorazole is a chemotherapeutic agent derived from metronidazole, with a notable trichomonocidal activity. It is used systemically, in giardiasis and intestinal amoebiasis.

Administration of nimorazole in pregnancy was neither embryofoetotoxic nor teratogenic [1,2,3,4,8]. Administration of oral doses of 250–500 mg/day for 6 days during various stages of pregnancy was harmless [4].

In the mouse, rat, and rabbit, nimorazole was without harmful effects [5,6,7]. In the mouse, oral doses of 5–20–80 mg/kg from the 6th to the 15th day of pregnancy were neither embryofoetotoxic nor teratogenic [5,6,7]. In the rat, oral doses of 25–250 mg/kg/day for the same period were likewise innocuous [5,6,7]. In the rabbit, oral doses of 50 mg/kg/day from the 6th to the 18th day of pregnancy had no adverse effects [5,6,7].

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Tenitrazole

α -thenoyl-amino-2-nitro-5-thiazole (MW 255.25)

Not contra-indicated in pregnancy.

Tenitrazole is a chemotherapeutic trichomonocidal drug derived from amino-nitrothiazole, and is more active on fungi and yeasts (*Candida albicans*). It is active orally, because it is rapidly absorbed via the intestinal route and eliminated in the urine, which it turns a characteristic yellow colour. Tenitrazole is used systemically or locally in the therapy of urogenital infections caused by *Trichomonas*, alone or in association with mycosis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, but the manufacturers recommend only topical application in pregnancy [1].

In the mouse, rat, and rabbit, tenitrazole caused foetal resorptions but was not teratogenic [2].

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Meparticine

particine methyl ester

Not contra-indicated in pregnancy.

Meparticine is a semi-synthetic polyene antibiotic obtained by esterification of a heptane macrolide (particine), isolated from the metabolic products of a strain of *Streptomyces auriofaciens*. It is used only topically in infections of mycotic and protozoal aetiology, particularly against *Candida albicans* and *Trichomonas vaginalis*.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3, 7, 8], and the manufacturers concur with this view [4]. It should be borne in mind that meparticine is not absorbed through the vaginal epithelium [5].

In the rat, meparticine was neither embryofetotoxic nor teratogenic [6]. Administration of 0.3–0.15–0.075% in the diet from mating until birth did not affect the incidence of foetal resorptions compared to controls, nor did it produce an increased malformation rate [6].

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Azanidazole

4-((E)-(1-methyl-5-nitro-1H-imidazol-2-yl)-ethenyl)-2-pyrimidine
(MW 246.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P				

To be used with care in pregnancy when given orally, but is not contra-indicated topically.

Azanidazole is an imidazole derivative with trichomonocidal activity, and is used both topically and systemically. Its principal pharmacological characteristic is the introduction of an amino group in position 2 of the pyrimidine ring.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1] when azanidazole is administered topically. We maintain that as this drug is a derivative of imidazole, it should be used with care when given orally in the first trimester, in the absence of sufficient evidence of safety.

In the rat and rabbit, azanidazole was neither embryofetotoxic nor teratogenic [2]. In the rat, administration of azanidazole from 340–3500 ppm in the diet from the 6th to the 15th day of pregnancy was not teratogenic [2]. In the rabbit, administration of 8–110 mg/kg/day from the 6th to the 18th day of pregnancy was not teratogenic and did not affect birth weight [2].

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7. AMOEBICIDAL CHEMOTHERAPY AND INTESTINAL ANTISEPTICS

Chemotherapeutic agents which act on protozoa and bacteria responsible for intestinal infections are generally only slightly soluble and thus not well absorbed. For this reason, their systemic action is not significant. Among such drugs are nitrofuranes (furazolidone) and the quinoline derivatives. The following drugs are discussed in this chapter:

	Recommendation	Page
Furazolidone	P	417
Clioquinol	P	418
Broxiquinoline	P	418
Fanquinone	NC	419

None of these drugs is contra-indicated in pregnancy. However, the prolonged use of halogenated compounds may be damaging to the foetal thyroid. We maintain that there is insufficient evidence available to make a reliable judgement on the following drugs in this group: chlorquinaldol, clefamide (see page 419).

Furazolidine

Furoxone,

N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidone (MW 225.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic			P		

To be used with care in pregnancy.

Furazolidone is a nitrofurane derivative with bacteriostatic and bacteriocidal activity towards numerous Gram-positive and Gram-negative strains. Given its slight water solubility, it is absorbed from the digestive tract to a very small extent, and is therefore used as an intestinal antiseptic.

The use of furazolidone in pregnancy is not contra-indicated, although it has, on rare occasions, caused neonatal haemolysis in the presence of congenital glucose-6-phosphate dehydrogenase deficiency [1, 2, 3].

Furazolidone has caused foetal resorptions, abortions, and reduced weight gain in the foetus in laboratory animals, when administered intra-aminotically

[4]. It appears that the drug acts both directly on the foetus, interfering with the Krebs cycle, and indirectly, by hormonal antagonism [4].

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Clioquinol

Barquinol, Propaderm, Synalar, Haelan, Betnovate, iodochloro-oxyquinoline (MW 305.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Clioquinol is a derivative of hydroxyquinoline, and has local antiseptic and amoebicidal actions.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1]. However, the prolonged use of clioquinol in pregnancy should be avoided because of its halogen content (see iodides, page 285).

No experimental studies have been described on the use of clioquinol in pregnancy in laboratory animals.

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- [1] *Dictionaire Vidal* - O.V.P. Ed. - Paris, 1975.

Broxyquinoline

dibromo-oxyquinoline (MW 302.97)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Broxyquinoline is an intestinal amoebicidal, bactericidal, and antifungal agent. It is often used in association with broxaldine in the therapy of amoebic dysentery. Broxyquinoline can cause optic atrophy [1].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [2]. However, the prolonged use of broxyquinoline in pregnancy should be avoided because of its halogen content (see bromides, page Vol. 1).

No experimental studies have been described on the use of broxyquinoline in pregnancy in laboratory animals.

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Fanquinone

4,7-phenanathronyl-5,6-quinone (MW 210.2)

Not contra-indicated in pregnancy.

Fanquinone is an amoebicidal chemotherapeutic which is used in both acute and chronic forms of amoebic dysentery and lambliaiasis.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2].

No experimental studies have been described on the use of fanquinone in pregnancy in laboratory animals.

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* * * * *

Chlorquinaldol

5,7-dichloro-8-hydroxyquinaldine (MW 228.07)

Quinaldol is an antibacterial and antifungal drug which is normally used as an intestinal antiseptic.

Clefamide

N-(β -oxyethyl)-*N*-(*p*-phenoxy(4'-nitro)-benzyl)-dichloro-acetamide (MW 399.25)

Clefamide is a synthetic drug which is only slightly toxic, and is active principally against amoebic infestations. It does not affect normal intestinal flora and is not appreciably absorbed. For this reason, it is ineffective in extra-intestinal amoebic infections.

We have been unable to obtain any information on the use of these drugs in pregnancy, either in the literature or from the manufacturers. Although there have been no reports of toxic effects, we believe that these drugs should be contra-indicated in pregnancy and in women of childbearing age who are likely to conceive.

8. ANTIHELMINTHIC CHEMOTHERAPY

There are numerous species of helminths, principally in the tropical regions, and there are as many categories of drugs which are suitable for use in such conditions. In Europe the most frequent forms encountered are the *Ascarides*, the *Taenia*, and the *Oxyuris*. The drugs most commonly used are piperazine, which is active against the *Ascarides*; niclosamide, active against *Taenia*; pirvinium, active against *Oxyuris*; gentian violet, active against *Oxyuris*; pirantel, active against the *Ascarides*; and oil of chenopodium, active against the *Ascarides*. Many of these drugs are absorbed in insignificant quantities from the digestive tract, as opposed to some others which are toxic to a greater or lesser extent, not only on the helminths but also towards the patient. The following drugs are discussed in this chapter:

	Recommendation	Page
Piperazine	NC	421
Niclosamide	NC	422
Pirvinium embonate	NC	422
Dithiazanine iodide	NC	423
Methylrosaniline	NC	423
Pirantel	NC	424
Oil of chenopodium	C	424

Only essential oil of chenopodium is contra-indicated in pregnancy, because of its toxicity. All the other antihelminthics listed are not contra-indicated. We maintain that there is insufficient information available for an accurate assessment of hexylresorcinol (page 424).

Piperazine

Antepar, Pripsin (MW 86.14)

Not contra-indicated in pregnancy.

Piperazine, in the form of various salts, is used to facilitate the expulsion of the helminths by blocking their motility. Its action occurs at the level of polarization of the muscle cells of the parasites. Its toxicity is very low. In addition to being an antihelminthic, piperazine has been used for a long time in the treatment of gout, where it helps to dissolve uric acid. It was later observed that its uricosuric effect was nonexistent.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 5, 6], although some authors have advised care in the use of piperazine [3, 4].

No experimental studies have been described on the use of piperazine in pregnancy in laboratory animals, and the manufacturers also have no information [17].

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Niclosamide

Yomesan,

N-(2'-chloro-4'-nitrophenyl)-5-chloro-salicylamide (MW 327.1)

Not contra-indicated in pregnancy.

Niclosamide is active against all forms of cestode infestation, and is also effective against *Taenia mana*, which is relatively resistant to other such drugs. It is not absorbed through the gastrointestinal mucosa and has no irritant effects.

Niclosamide has been used in pregnancy without maternal or foetal side effects [2]. Administered to three patients during labour, it did not have any harmful effect [2]. The use of niclosamide in two patients in the 1st and 7th months of pregnancy was without adverse effects in the mother or the foetus [3].

No experimental studies have been described on the use of niclosamide in pregnancy in laboratory animals.

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Pirvinium embonate

bis-6-dimethylamino-2-(2-(2,5-dimethyl-1-phenyl-3-pyrrolyl-vinyl)-1-methyl-quinoline salt of 4,4'-methylene-bis(3-hydroxy-2-naphthoic) acid (MW 1151.4)

Not contra-indicated in pregnancy.

Pirvinium is the salt of a colouring agent belonging to the cyanine group. It is administered exclusively by the oral route, and acts only in the gastrointestinal tract, from which it is not absorbed, and does not pass into the

circulation in appreciable amounts. At effective therapeutic doses, the toxicity of pirvinium is negligible.

Pirvinium has been administered in pregnancy with no adverse effects on the mother, the foetus, the neonate, or the suckling infant [1].

No experimental studies have been described on the use of pirvinium in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta Parke-Davis - Milano.

Dithiazanine iodide

3,3'-diethylthiodicarbocyanine iodide (MW 518.5)

Not contra-indicated in pregnancy.

Dithiazanine is effective principally in infestations of *Ascaris lumbricoides*, *Trichiuris trichiura*, *Strongyloides stercoralis*, and *Oxyuris vermicularis*, and is a colouring agent of the cyanine group. It is very slightly absorbed from the gastrointestinal mucosa, and eliminated in the faeces, which are coloured blue. Its mechanism of action is via interference with processes regulating oxygenation and metabolism in the helminths.

No harmful effects have been reported on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1].

No experimental studies have been described on the use of dithiazanine in pregnancy in laboratory animals. However, no contra-indications have been indicated in veterinary medicine, where the drug is commonly used in numerous animal species (horse, dog, cat, pig, rabbit, ruminants, baboon, monkey, zebra) [2].

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Methylrosaniline or gentian violet or methyl violet or crystal violet

(MW 408.0)

Not contra-indicated in pregnancy.

Methylrosaniline is active against Gram-positive bacteria and many species of fungi, as well as being antihelminthic.

Oral administration results in only slight absorption through the gastrointestinal mucosa, and therefore there is little risk of damage to the foetus [1].

No experimental studies have been described on the use of methylrosaniline in pregnancy in laboratory animals.

Bibliography

[1] Comunicazione personale della Ditta Violani-Farmavigor - Milano.

Pirantel pamoate or embonate

(MW 594.7)

Not contra-indicated in pregnancy.

Pirantel is an antihelminthic active against ascarides, ankylostoma, and *Anterobius vermicularis*. It can cause nausea, vomiting, and increase in serum transaminase levels.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2].

No experimental studies have been described on the use of pirantel in pregnancy in laboratory animals.

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Essential oil of chenopodium

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Oil of chenopodium is obtained by steam distillation of the fresh plant of *Chenopodium ambrosiodes*, and is used to expel ascarides. Its toxicity is manifested by central nervous system disturbance and damage to the liver and kidneys. For this reason, oil of chenopodium should be avoided in young children, the elderly, those already debilitated by illness, and those with hepatic or renal disease.

Oil of chenopodium is contra-indicated in pregnancy because of its high toxicity.

No experimental studies have been described on the use of oil of chenopodium in pregnancy in laboratory animals.

* * * * *

Hexylresorcinol

(MW 194.3)

Hexylresorcinol is active against infestations of ascarides, oxyurides, and diphyllobothrium. It has weak antibacterial activity and is also used as a spermicide. It is very slightly absorbed from the intestine, but possesses considerable irritant effects on the mucosa and is therefore contra-indicated in gastroenteritis.

We have been unable to obtain any information on the use of this drug in pregnancy, either in the literature or from the manufacturer. In the absence of sufficient evidence of its safety, we recommend that it should be avoided where possible in pregnancy and in women of childbearing age who are likely to conceive.

9. ANTIMALARIAL CHEMOTHERAPY

The antimalarial drugs, the schizonticides or gametocides, have a structure related to quinoline, acridine, biguanide, or diaminopyrimidine. The salts of quinine are schizonticides and gametocides, as are the derivatives of the aminoquinolines, chloroquine and hydroxychloroquine. Among the diaminopyrimidines, it is worth mentioning pyrimethamine, which is used in the treatment of toxoplasmosis, and trimethoprim (see page 385). The following drugs are discussed in this chapter:

	Recommendation	Page
Quinine sulphate	P	426
Chloroquine phosphate	P	429
Hydroxychloroquine sulphate	P	430
Pyrimethamine	C (C during lactation)	431

During pregnancy it is advisable to avoid the use of these drugs because of their embryofetotoxic effects. Pyrimethamine is contra-indicated, while quinine, chloroquine, and hydroxychloroquine, according to some authors, require less drastic limitations.

Quinine sulphate

quinine salt of 3-carboxy-salicylic acid (MW 783.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute				P	
Chronic	P	P	P		

To be used with care in pregnancy.

Quinine is an alkaloid extracted from the plant *Cinchona*, and represents the laevorotatory stereoisomer of quinidine. Quinine has irritant and anaesthetic local effects. It is used mainly as an antimalarial (schizonticide and gameticide), and is also an analgesic and antipyretic, with a central mechanism similar to that of the salicylates, as well as having a curare-like effect on smooth muscle. The action of quinine on the heart is similar to that of quinidine (see Vol. 1). It has an oxytocic action on the pregnant uterus, which can only partly explain its abortive effects, which are probably related to its embryofetotoxic action.

Quinine is administered only orally, and because of its irritant action, the intramuscular route is contra-indicated. It is rapidly absorbed and is largely bound to plasma proteins. It is eliminated mainly in the urine, in its hydroxylated form.

Quinine is essentially a cytoplasmatic, particularly for unicellular organisms, including spermatozoa. Its toxicity is particularly evident on the optic and acoustic nerves, on medullary haemopoiesis, on the kidney, and on prothrombin synthesis. The therapeutic use of quinine is actually very limited.

Quinine crosses the placental barrier [2,10,15,16,17,18]. During the first trimester, quinine at therapeutic doses does not produce foetal malformations [1,52], although at high doses it is embryofetotoxic. It damages the central nervous system, in particular the retina and the organ of Corti [2]. Its toxicity may lead to the death of the embryo and its abortion [3,4,5,6,7,8,9,47,53]. When pregnancy continues, teratogenic effects may be observed, particularly in the central nervous system, the eye [10,11,49], the ear [10,11] with deafness at birth, the limbs [14], the cranium [3,14], and the abdominal wall [14]. According to other authors, the incidence of such malformations is not significant [10].

In the third trimester, quinine is not teratogenic but is foetotoxic, with possible deafness at birth [10,19,21,41,42,43,44]. Other authors doubt this [23,24,51]. At high doses, toxic effects are also controversial [16,25]. Independently of its effects on the embryo and the foetus, quinine can stimulate contractions of uterine muscle and cause abortion [14,54].

In labour, quinine can give rise to frequent emissions of meconium. It has not been established whether this is the consequence of direct action on the foetal intestine of the consequence of foetal distress [25]. The neonate may suffer damage to the ear, as has already been mentioned, together with the appearance of thrombocytopoenic purpura [4,5,6,20,21,22,23,24,26,45,46,50,54,55]. These manifestations also occur in the mother [4,5,6].

Small amounts of quinine were found in milk some hours after administration [27,28]. Even though at therapeutic doses quinine appears to be harmless, at high doses there are signs of embryotoxic, foetotoxic, and teratogenic actions.

In the rat, mouse, rabbit, guinea-pig, dog, and monkey, inconclusive results have been obtained on the effects of quinidine administration. In the rat, oral or intramuscular doses of 10–100 mg/kg from the 4th to the 18th day of pregnancy were not teratogenic. Foetotoxic effects were dubious [29,30,31]. In the mouse, oral doses of 125–500 mg/kg from the 6th to the 12th day of pregnancy were not teratogenic but were foetotoxic [32].

In the rabbit, oral or subcutaneous doses of 65–325 mg/day from the 10th to the 28th day of pregnancy were teratogenic (malformations of the ear, with degeneration of the acoustic nerve, and of the spinal ganglia, and exencephalia) and foetotoxic [31,33,34,35]. In the guinea-pig, subcutaneous doses of 200–1300 mg/day at various stages of pregnancy were teratogenic (cochlear

lesions) [36,37]. In the dog, intramuscular doses of 15–50 mg/kg from the 18th to the 48th day of pregnancy were foetotoxic [31]. In the monkey, oral doses of 20–200 mg/kg from the 21st to the 29th day of pregnancy were neither foetotoxic nor teratogenic [38].

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Chloroquine phosphate

7-chloro-4-(4'-diethylamino-1'-ethyl-butylamino)quinoline (MW 515.9)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P				

To be used with care in pregnancy.

Chloroquine, a derivative of aminoquinoline, is an antimalarial active against the schizonts present in the erythrocytes. It suppresses the acute attacks caused by all types of malarial parasites, but it does not eliminate the forms within the erythrocytes, nor does it eliminate the gametes. The mechanism of action of chloroquine is not well understood. It is known that it inhibits the synthesis of DNA and also of RNA, and the accumulation of the drug in the red cells of the parasite may explain its schizonticidal mechanism.

Although it has been studied primarily as an antimalarial, chloroquine also possesses anti-inflammatory, anti-arrhythmic, and anaesthetic properties, and in high concentrations it is an anticoagulant. It is also useful in the therapy of photo-allergic reactions.

Transplacental passage of the drug has been demonstrated in the mouse, and it accumulates in the foetus, particularly in the eyes [3,14]. It is thought that chloroquine should be administered with care in women of childbearing age, and is contra-indicated in pregnancy because it causes foetal damage [2,11,12,13,14,15]. A patient with lupus erythematosus, who periodically took chloroquine, gave birth to three malformed infants, two with cochlear-vestibular paresis and one with a Wilms tumour. She also had one miscarriage. In three successive pregnancies in which she did not take chloroquine, the infants were healthy [2]. In another case involving treatment with chloroquine in pregnancy, a complete cochlear lesion was observed in the neonate [11].

In other investigations, it was concluded that administration of chloroquine in pregnancy did not give rise to side effects in the foetus [4, 5, 7, 8, 9, 10, 16]. A patient with lupus erythematosus, following two miscarriages, was treated during the third pregnancy with chloroquine. The infant was normal, with no malformations [8]. Three patients with rheumatoid arthritis conceived during therapy with chloroquine, which was continued throughout pregnancy. There were no foetal side effects [9]. In 17 patients with lupus erythematosus treated during one or more pregnancies with chloroquine and other drugs (cortisones, salicylates), there was no damage to the foetus [10]. There was no damage to the auditory nerves in a 14-week foetus, although the mother had taken hydroxychloroquine at a dose of 400 mg/day during the first weeks of pregnancy [5].

In the rat and mouse, chloroquine was embryofetotoxic and teratogenic [3, 6]. Accumulation of the drug in the retina, which was observed in the mouse, indicated a possible foetal risk to the use of the drug in pregnancy [3]. In the rat, a dose of 1 g on the 9th day of pregnancy was embryofetotoxic and teratogenic [6]. In the mouse, intravenous administration of labelled drug caused ocular damage in the foetus [3].

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Hydroxychloroquine sulphate

Plaquenil (MW 434.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P				
Chronic	P				

To be used with care in pregnancy.

Hydroxychloroquine is a derivative of chloroquine, of which it retains the

principal characteristics (see page 429), including accumulation in the tissues. Hydroxychloroquine is used mainly in the treatment of rheumatoid arthritis, lupus erythematosus, and malaria.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and the manufacturers concur with this view [1]. Other authors [2, 3] advise care in the use of hydroxychloroquine in pregnancy because of possible toxic effects. However, it should be emphasized that chloroquine, from which hydroxychloroquine is derived, crosses the placental barrier, and may thus cause cochlear-vestibular lesions in the foetus (see chloroquine, page 429).

No experimental studies have been described on the use of hydroxychloroquine in pregnancy in laboratory animals.

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Pyrimethamine

Daraprim, Fansidar, Maloprim,

2, 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine bitartrate (MW 248.71)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	C	C	C		C

Contra-indicated in pregnancy and during lactation.

Pyrimethamine is a synthetic antimalarial drug with a diaminopyrimidine structure, which is used in the therapy of toxoplasmosis. Its mechanism of action involves inhibition of folic acid synthesis in the parasite.

The use of pyrimethamine in pregnancy is not advised, because of its embryofoetotoxic and teratogenic effects [1, 2, 3, 4, 7, 8]. Pyrimethamine is also contra-indicated during lactation, because it passes into breast milk, where it reaches maximum levels 6 hours after ingestion [5]. It can prevent malaria in the suckling infant [9].

No experimental studies have been described on the use of pyrimethamine in pregnancy in laboratory animals.

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10. BISMUTH SALTS

Salts of bismuth

basic bismuth salicylate, heptadienecarbonate of bismuth

Not contra-indicated in pregnancy.

Salts of bismuth have a spirochaeticidal action, and were widely used in antilutic therapy because they were efficacious and less toxic than the arsenicals, before penicillins became available. Since the action of bismuth is gradual, a cycle of treatment with salts of bismuth in late syphilis is still used today before resorting to penicillin, in order to avoid a Herxheimer reaction. Salts of bismuth are also used in association with antibiotics in the therapy of inflammation of the appendix, the tonsils, and the teeth, whether this is mixed or spirillar in form.

No foetal damage resulting from the administration of bismuth in pregnancy has been reported [1]. Since a vast amount of information has been accumulated over many years to amply validate its safety in pregnancy, there is no need for its contra-indication.

In the chicken and sheep, bismuth was neither embryofetotoxic nor teratogenic [2, 3]. In sheep, a dose of 5 mg/kg throughout pregnancy caused arrested growth and exophthalmia in only one foetus, an insignificant incidence [2]. No malformations were found in chick embryos injected with bismuth into the yolk sac from the 4th to the 8th day of incubation [3].

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Bismuth camphocarbonate

(MW 794.7)

Not contra-indicated in pregnancy.

Bismuth camphocarbonate has an antispirillar action and is used in tonsillitis and infective angina. It is a soluble compound of bismuth, and as such crosses the placental barrier and is found in foetal blood [1, 2].

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy. However, the manufacturers advise against the use of bismuth camphocarbonate in pregnancy, although they do not give any reasons [3].

No experimental studies have been described on the use of bismuth camphocarbonate in pregnancy in laboratory animals.

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11. ANTINEOPLASTIC CHEMOTHERAPY

The chemotherapy of malignant tumours is based on the supposition that neoplastic cells have biological characteristics which differ from normal cells. Oncochemotherapeutic drugs may be subdivided on the basis of their mechanism of action and their origin into alkylating agents, antimetabolites, antibiotics, etc., or on the basis of the type of cytostasis which they achieve.

Some drugs act in a less specific manner on almost all cells, while others act only on cells in the reproductive phase, i.e., they act specifically on the cell cycle. Among the latter, there are some which interfere only with one phase of the cell cycle. This allows the study of suitable combinations of drugs which take into account the different mechanisms of action, thus leading to polytherapy in which individual drug actions are potentiated.

The use of oncochemotherapeutic drugs which are phase-specific, which block and then synchronize all the cells in a single phase of the reproductive cycle, makes it possible to administer such drugs in successive periods of the cell cycle. In this way, the cytotoxic effects of drugs on neoplastic cells may be further improved when the duration of the cell cycle is known. Thus a sequentially synchronized polytherapy is achieved, which represents the most advanced form of treatment of fast-growing tumours. In slowly developing tumours, on the other hand, the physician relies mainly on administration of nonspecific drugs such as the alkylating agents, since the cells which are reproducing at any one time are relatively few.

The following drugs are discussed in this chapter:

	Recommendation	Page
<i>Alkylating agents</i>		
Busulphan	C	437
Chlorambucil	C	439
Cyclophosphamide	C	440
Melphalan	C	442
Polymelphalan	C	442
Thiotepa	C	443
Chlormetin hydrochloride	C	444
Carmustine	C	445
<i>Antimetabolites</i>		
Mercaptopurine	C	446
Azathioprine	C	448
Thioguanine	C	450
Amethopterin	C	451

Fluorouracil	C	453
Cytarabine hydrochloride	C	454
<i>Miscellaneous antineoplastic agents</i>		
Actinomycin D	C	456
Mitomycin	C	457
Bleomycin	C	458
Daunomycin	C	459
Adriamycin	C	459
Vincristine sulphate	C	460
Vinblastine	C	461
Procarbazine hydrochloride	C	462
Asparaginase	C	463
Pipobromane	C	464
Hydroxycarbamide	C	465

The alkylating agents, antimetabolites, alkaloids, antibiotics, and various other antineoplastic drugs are all contra-indicated in pregnancy. This does not mean that they cannot be used when absolutely necessary, when the life of the mother is at stake, or in the interest of the foetus (immunosuppression in cases of serious maternal foetal iso-immunization or of renal transplants), so that the pregnancy may be continued until the foetus is viable, without compromising the health of the mother. However, this contra-indication should be carefully evaluated by the physician in consultation with the mother, because these drugs are clinically indicated in types of leukaemia and systemic malignant neoplasia, and they are often indispensable. It is therefore necessary to attempt to reconcile the interests of the mother and the foetus, without sacrificing one to save the other. This requires careful discussion between the patient and the physician of all the consequences of treatment.

After the first half of pregnancy, there should be no teratogenic effects, although antineoplastic drugs may still be embryofetotoxic, with the retardation of somatic development and depression of the foetal immune system. After the birth, usually within a short time, growth and development should revert to normal.

Similar treatments therefore carry a calculated risk which is far inferior to the damage resulting from a serious maternal-foetal iso-immunization or the dramatic development of a neoplastic disease, which can even prevent a live birth. In our opinion, antineoplastic drugs are contra-indicated in pregnancy, but their frequent use in the first half of pregnancy may often be justified, and this should be discussed with the mother.

At this point, other aspects of the problem should be mentioned, such as whether or not the pregnancy should be allowed to continue in these circumstances. In the event of a pregnancy developing during treatment with a

combination of antineoplastic drugs, which can greatly potentiate individual teratogenicity, or of a pregnancy going unrecognized during treatment, we believe that the possibility of therapeutic abortion should be discussed with the patient. It would be advisable, because of the risks involved, for suitable contraceptive methods to be used, or to carry out sterilization of the patient in the case of neoplastic disease or antilastic treatments.

11.1 Alkylating agents

Busulphan

Myleran, 1, 4-dimethanosulphonxybutane (MW 246.31)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Busulphan is an alkylating methanesulphonate with specific myelo-suppressant activity and is used principally in the treatment of chronic myeloid leukaemia.

Busulphan crosses the placental barrier [1]. Administration of the drug in pregnancy causes teratogenic effects on the eye (microphthalmia, corneal opacity), the palate (cleft palate), the gonads (hypoplasia with changes in germinal cells and consequent sterility), the thyroid (hypoplasia), and in all cells of the organism (cytomegaly with enormous increase in nuclear volume) [1, 2, 3, 19, 24, 25, 27, 28, 31, 32]. Busulphan is also embryofetotoxic, causing arrest of foetal growth [1, 5, 20, 26, 32].

Some doubt has been expressed concerning the relationship of these effects to the administration of busulphan in pregnancy [4]. There have been reports of some cases where treatment in pregnancy caused no harmful effects on the foetus [6, 7, 17, 29, 30]. Administration of busulphan at a dose of 4–6 mg/day for 5 weeks from the 2nd to the 3rd months to a pregnant woman with chronic myeloid leukaemia was without foetal side effects [6]. In a patient affected with chronic myeloid leukaemia, administration of the drug at a dose of 4–6 mg/day, from the 7th to the 9th month of pregnancy, did not damage the foetus [7]. Administration of busulphan at doses of 2–6 mg/day on the first trimester to nine pregnant women with chronic myeloid leukaemia was without harmful effects [17]. A patient with chronic myeloid leukaemia treated with busulphan at doses of 2–4 mg from the 8th week of pregnancy until term had a normal infant [29]. Similarly, in another patient with the same disease treated with

busulphan at doses of 2–8 mg during the first 6 weeks of pregnancy, and then from the 9th to the 13th week, the infant was healthy [30].

In the rat and mouse, busulphan had embryofetotoxic and teratogenic effects which were dependent on gestational age [4,8,11,13,15,16,22,23]. Administration of the drug in pregnancy caused sterility or infertility in the offspring [9,10]. In the rat, doses of 18–34 mg on the 12th day of pregnancy caused cleft palate and malformations of the toes [11]. A dose of 25–50 mg/kg intraperitoneally from the 9th to the 15th day of pregnancy was embryofetotoxic and teratogenic, producing exencephaly, phocomelia, and oligodactyly [13]. At doses of 15 ppm in the diet throughout pregnancy, busulphan was fetotoxic and teratogenic [15]. In the mouse, oral doses of 100–250 mg from the 7th to the 11th day of pregnancy were teratogenic [16].

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Chlorambucil or chloraminophen

Leukeran,

N,N-di(2-chloroethyl)-*p*-aminophenylbutyric acid (MW 304.23)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Chlorambucil is a nitrogen mustard which possesses alkylating activity. It is not very toxic, and is used principally in chronic lymphatic leukaemia and in Hodgkin's disease.

When administered in the first months of pregnancy, chlorambucil had an embryofoetotoxic action which could lead to abortion, and was also teratogenic, particularly in the urinary tract [1, 2, 3, 4, 5, 6, 18, 22, 23, 26]. A patient with Hodgkin's disease treated with chlorambucil at a dose of 6 mg/day from the 5th to the 11th week of pregnancy, produced an infant with agenesis of the kidney and left ureter [18]. According to various authors, the teratogenic action of chlorambucil ceases after the first trimester of pregnancy, but its foetotoxic action persists, and is manifested by retardation of foetal development [8, 9, 24].

In the rat and mouse, chlorambucil was teratogenic if administered in the initial stages of pregnancy [10, 11, 12, 13, 14, 16, 17, 20, 21, 27]. In the rat, doses varying between 6 and 12 mg/kg given on the 12th day of pregnancy caused skeletal anomalies, including syndactyly and cleft palate [10, 11, 12, 13, 14], while 6 mg/kg on the 10th day of pregnancy caused malformations of the urogenital tract in 95% of foetuses [16, 17]. A single intraperitoneal dose of 6 mg/kg was embryofoetotoxic and teratogenic, causing oligodactyly, syndactyly, cleft palate, alterations in the toe and the urogenital tract [20]. In the mouse, doses of 5–10 mg/kg intraperitoneally from the 7th to the 12th day of pregnancy were embryotoxic and teratogenic, producing malformations of the limbs and urogenital tract [21].

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Cyclophosphamide

Cyclophosphamide, Endoxana,

N,N-bis-(β -chloroethyl)-*N'*, *O*-propylenediamide of phosphoric acid

(MW 279.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Cyclophosphamide is an alkylating agent with selective action on neoplastic tissues. It must first be activated by the enzyme systems present in high concentrations in neoplastic cells and in the placenta [12]. Cyclophosphamide not only blocks replication of DNA, but has a notable cytotoxic effect which leads to inhibition of various cellular functions such as glycolysis, the pentose cycle, respiration, and protein synthesis.

Cyclophosphamide administered in the first month of pregnancy can be embryofoetotoxic and teratogenic. In the literature, there have been reports of skeletal malformations of the extremities, arrest of intra-uterine growth, and death of the foetus [1, 2, 3, 4, 5, 6, 7, 8, 18, 23, 27]. According to other authors, use of cyclophosphamide after the first trimester of pregnancy in the treatment of malignant neoplasms [16, 24], or as an immunosuppressant in isoimmunization of the maternal-foetal RH type [17], should not have embryofoetotoxic or teratogenic effects.

Cyclophosphamide passes into breast milk [25], and can cause bone marrow depression in the infant [26].

In the rabbit, chick embryo, rat, and mouse, cyclophosphamide administered in the early stages of gestation was teratogenic [9,10,11,13,21,22]. In chick embryo, injection of the drug on the 11th day of incubation at a dose of 0.1 mg caused 60% mortality and 30% malformations, including global hypotrophy, brachymelia, parrot beak, absence of eyelids, and visceral (particularly cardiac) lesions [10]. Treatment on the 12th day led to 47% malformations, while administration on day 14 caused 77% mortality and 20% malformations [11].

In the rat, doses of 7–10 mg/kg on the 11th and 12th days of pregnancy caused malformations of the skeleton, cleft palate, exencephaly, and encephalocele [13]. In the rabbit, intravenous doses of 30 mg/kg from the 6th to the 14th day of pregnancy were embryofetotoxic and teratogenic, causing umbilical hernia, phocomelia, oligodactyly, cleft palate, and anomalies of the tail [21]. Complete disappearance of the foetal gonocytes could occur following treatment with cyclophosphamide in pregnancy [9].

In the mouse, a dose of 20 mg/kg intradermally from the 9th to the 14th day of pregnancy was embryofetotoxic and teratogenic (exencephaly, ocular malformations, polydactyly, phocomelia, cleft palate, anomalies of the tail and the urogenital tract) [22].

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Melphalan

Alkeran, *p*-di-(2-chloroethyl)-amino-L-1-phenylalanine (MW 305.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Melphalan is a derivative of phenylalanine, and an alkylating agent which possesses cytotoxic activity similar to that of the nitrogen mustards. It causes the formation of bridges between molecules of DNA during the intermitotic phase of the cell cycle.

According to some authors, melphalan is contra-indicated in pregnancy [1,2]. Others believe that it should be used with care, particularly in the first trimester, because its safety regarding the foetus has not been sufficiently established [3]. Given its mechanism of action, we believe that melphalan should be contra-indicated, especially in the first trimester, as are all alkylating agents.

No experimental studies have been reported on the use of melphalan in pregnancy in laboratory animals.

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Polymelphalan

6 synthetic peptides conjugated by covalent links with *m*-(di-(2-chloroethyl))amino-L-phenylalanine (meta-L-sarcosine)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Polymelphalan is an alkylating agent obtained by inserting sequences

of amino acids into *m*-2-chloroethylamino-L-phenylalanine, where they are attached to the amino and carboxylic groups (in melphalan, the dichloroethylamino group is in the para instead of the meta position). In this way, the therapeutic activity of the alkylating group may be potentiated by an increased selectivity for the neoplastic cells, which generally are more dependent on a supply of amino acids than are normal cells.

The same considerations apply to the use of polymelphalan in pregnancy as have been outlined for melphalan (see page 442).

Polymelphalan was teratogenic in the rabbit and reduced fertility in the rat. In the rat, doses of 0.5–1 mg/kg given six times from the 7th to the 18th day of pregnancy did not cause obvious foetal malformations. A dose of 0.5 mg/kg in males and 0.76 mg in females, given five times before mating, reduced fertility and increased postnatal mortality [1]. In the rabbit, polymelphalan administered seven times at a dose of 1 mg/kg from the 14th to the 16th day of pregnancy caused foetal malformations [1].

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Thiotepa

Lederle, *N,N',N''*-triethylenethiophosphoramide (MW 189.23)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Thiotepa is an alkylating agent, a substance which contains a highly reactive alkyl group which can react with numerous molecules of fundamental biological importance. Its sphere of activity in inhibiting cellular replication is thus very large, and it is regarded as a nonspecific cell cycle inhibitor.

Thiotepa has been widely used in the treatment of ovarian, mammary, bronchial, and digestive tract carcinomas, and in numerous other solid tumours. It also produces remission in chronic leukaemia, in myeloma, in Hodgkin's disease, and in reticulo- and lympho-sarcoma.

Thiotepa is contra-indicated in pregnancy [1]. However, cases have been reported of patients who have taken the drug in the first trimester without adverse consequences to the foetus [2,11].

In the rat, mouse, and chick embryo, thiotepa was foetotoxic and teratogenic [3,4,5,7,8,9,10]. In the rat, subcutaneous doses of 3–7 mg/kg given in a

single administration from the 8th to the 16th day of pregnancy were foetotoxic and teratogenic (hydrocephaly, gastroschisis, anomalies of the eye, mouth, tail, cranium, oedema, phocomelia, oligodactyly) [3]. At doses of 5 mg/kg given in a single administration on the 12th day of pregnancy, thiotepa caused the death of about 50% of fetuses. In the remaining animals, there were obvious signs of foetotoxic and teratogenic activity [4]. In a further study, it was shown that two injections per day of 5 mg/kg each were sufficient to cause foetal resorptions and malformations [5].

In the mouse, an intraperitoneal dose of 5–20 mg/kg from the 6th to the 15th day of pregnancy was foetotoxic and teratogenic (exencephaly, spina bifida, gastroschisis, polydactyly, phocomelia, oligodactyly, oedema, anomalies of the tail) [7]. In chick embryo, a dose of 0.01 mg given on the 14th day of incubation was not teratogenic [5].

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Chlormetin hydrochloride or mustin or chloretazin or mecloretamine or nitrogen mustard or HN2

methyl-bis-(β -chloroethyl)-amine hydrochloride (MW 192.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Chlormetin is an alkylating agent, and binds to the DNA molecule and to cell proteins in general, inhibiting cellular replication and causing chromosome damage and mutagenic effects [1, 2].

No reports of harmful effects on the human foetus, the mother, or the pregnancy have, in fact, been found [3, 4]. However, we believe that the use of chlormetin in pregnancy is contra-indicated because of its mechanism of action.

No experimental studies have been described on the use of chlormetin in pregnancy in laboratory animals.

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Carmustine or BCNU

BiCNU, 1,3-di(2-chloroethyl)-1-nitrosourea (MW 214.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Numerous derivatives of nitrosourea have antiblastic activity, particularly the *N*-alkyl-*N*-nitrosoureas. The carbonium ions generated by these substances react with many chemical groups present in biological molecules, particularly the nucleic acids. Carmustine inhibits RNA and DNA synthesis, slowing nucleotide transferase activity and increasing NAD-ase, especially in cells which are actively dividing. Carmustine has only slight specificity for a particular phase in the cell cycle. This mechanism of action is also the basis for its effects on mutagenesis and on teratogenesis.

Carmustine is rapidly absorbed from the digestive tract, metabolized, and excreted in the urine. It rapidly diffuses through the central nervous system. Its toxic effects occur mainly in bone marrow, liver, and kidneys.

No harmful effects on the human foetus, the mother, or the pregnancy have, in fact, been reported. However, we maintain that the use of carmustine in pregnancy is contra-indicated, because of its mechanism of action.

In the rat and rabbit, carmustine was embryotoxic and teratogenic only at high doses [1]. In the rat, intraperitoneal doses of 0.25–0.75–1.5 mg/kg/day both before and until the 20th day of pregnancy were embryotoxic at the higher doses. Intraperitoneal doses of 1.5–2–4 mg/kg/day during the period of organogenesis were teratogenic, causing defects of thoracic–abdominal closure, anomalies of the eye, and of the central nervous system. Intraperitoneal doses of 0.025–0.75–1.5 mg/kg/day from the 15th day of pregnancy until the 21st day after parturition were not harmful to the mother or the foetus [1]. In the rabbit, intravenous doses of 0.05–1.4–4 mg/kg/day from the 6th to the 18th day of pregnancy were toxic to the mother and to the embryo only at the higher doses [1].

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11.2 Antimetabolites

Mercaptopurine

Puri-Nethol (MW 170.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Mercaptopurine is an analogue of both adenine and hypoxanthine, and must be converted within the cell into the corresponding ribonucleotide before being able to act biologically. It possesses a dual mechanism of action: (1) It interferes with the conversion of inosinic acid to adenylic and guanylic acids; (2) It inhibits the synthesis of purines by inhibiting a pseudo-feedback mechanism (excessive concentrations of the antimetabolite inhibit a preceding step in the biosynthesis of the true metabolite).

Mercaptopurine is embryofetotoxic and teratogenic, although the degree to which it is harmful is directly related to the gestational age at which therapy is initiated. In early pregnancy, mercaptopurine may cause abortion [1, 2] or the appearance of malformations [1, 3, 4, 5, 6, 7, 8, 35, 38]. After the first trimester, the use of mercaptopurine in the treatment of malignant tumours, or as an immunosuppressant in serious maternal-foetal Rh isoimmunization, may be innocuous [8, 9, 10, 16, 17, 18, 19, 20, 27, 28, 29, 30, 31, 32, 33, 34, 36, 37, 40], or may, at most, cause a retardation of intra-uterine foetal development [3]. The case has been reported of a patient who took mercaptopurine throughout pregnancy. The infant was premature and anaemic, but had no malformations [17]. The infants of 5 patients treated with the drug after the first trimester were normal [18].

Four neonates of patients treated from the 28th week onwards with doses of 100 mg/day presented at birth with a Heiniss quotient greater than 0.8 (real weight/theoretical weight). There was no hypodystrophy in the infants, but they had deficiencies of IgA, IgM, and IgG compared to controls [19]. Two infants of isoimmunized mothers treated from the 6th month of pregnancy at a dose of 50 mg/day had normal haemoglobin levels and no malformations [20]. In a pregnant woman with melanosarcoma, administration of 6-mercaptopurine in the 6th month of pregnancy at a total dose of 500 mg in 12 days, in association with amethopterin and phosphorus-32, was without embryofetotoxic or teratogenic effects [29]. Administration of the drug to 15 isoimmunized pregnant women at doses of 50 mg/day in the 3 months preceding birth did not cause foetal damage [31]. In three isoimmunized pregnant women, administration of

mercaptopurine from the 7th to the 9th month of pregnancy at a dose of 150 mg/day was without harmful effects [32].

In the rat, mouse, rabbit, and chick embryo, mercaptopurine had embryo-foetotoxic and teratogenic effects [11,12,13,14,15,22,23,39]. In the rat, oral doses of 5–10 mg/kg caused the interruption of pregnancy in 100% of cases [11,12]. Intraperitoneal administration, however, caused the appearance of malformations in the central nervous system [11,13]. In the same animal, the drug often produced spontaneous abortion [14]. If administered from the 5th to the 9th day of pregnancy at doses of 4–75 mg/kg, it caused malformations of the central nervous system [13]. Intraperitoneal doses of 62.5 mg/kg on the 11th day of gestation were foetotoxic and teratogenic causing cleft palate, and malformations of the tail and urogenital tract [21].

In the chick embryo, mercaptopurine caused retardation of central nervous system development [15]. In the mouse, doses of 0.5–1 mg/kg from the 6th to the 8th day of pregnancy were foetotoxic and teratogenic [22]. In the rabbit, subcutaneous doses of 1 mg/kg from the 6th to the 9th or from the 10th to the 14th day of pregnancy were foetotoxic and teratogenic, causing spina bifida and malformations of the limbs [23].

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Azathioprine

Imuran, 6-(1-methyl-4-nitro-5-imidazolyl)-thiopurine (MW 277.29)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Azathioprine is a purine antimetabolite, derived from 6-mercaptapurine. It has the same mechanism of action, but is more slowly metabolized. At the cellular level, azathioprine has two principal actions: it interferes with transformation of inosinic acid to adenylic and guanylic acids, and it inhibits the synthesis of the purines by means of an inhibitory pseudo-feedback action (excessive concentrations of the antimetabolite inhibit a preceding step in the biosynthesis of the real metabolite). Azathioprine is used mainly as an immunosuppressant in organ transplantation and in autoimmune diseases.

Azathioprine crosses the placental barrier [1]. Studies on possible foetal damage caused by the drug when administered in pregnancy are controversial. Azathioprine has been administered continuously as an immunosuppressant in renal transplantation with supervening pregnancy, without harmful effects on the foetus [2,3,4,5,6]. Administration of the drug at doses of 75 mg/day throughout pregnancy to a patient who underwent homologous renal transplantation and became pregnant 5 months later did not adversely affect the foetus [3].

Some authors, however, emphasize the danger of azathioprine to pregnant women undergoing renal transplantation, because of possible toxic effects on the foetus [8,9,10,20,21]. Administration of 75-100 mg/day throughout

pregnancy to a patient who underwent renal transplantation caused foetal chromosome damage (rupture, translocation, deletion), although there were no physical malformations in the neonate [8].

Azathioprine has been used with some success in the treatment of severe Rh isoimmunization, without adversely affecting the foetus [11,17]. Used in small doses for long periods (1 mg/kg/day) after the 20th week of pregnancy, the drug did not cause marked foetal damage, while it reduced or even eliminated the consequences of maternal isoimmunization [11]. Administration of azathioprine to an isoimmunized patient from the 7th to the 9th month of pregnancy at doses of 150 mg/day did not have embryofoetotoxic or teratogenic effects [17].

In the rat, mouse, rabbit, and dog, azathioprine was embryofoetotoxic [19] and teratogenic [12,13,14,15,16,18]. In the rat, oral doses of 10–40 mg/kg from the 10th to the 15th day of pregnancy were embryofoetotoxic and teratogenic [12]. Oral doses of 1–10–25 mg/kg from the 6th to the 15th day of pregnancy increased the incidence of spontaneous abortions and deceased neonatal vitality, but were not teratogenic [19].

In the mouse, intraperitoneal doses of 4–30 mg/kg given at various stages of pregnancy caused alterations of the skeleton, central nervous system, eyes, limbs, mouth, thymus, and skin [13,14]. In the rabbit, oral doses of 10 mg/kg from the 6th to the 14th day of pregnancy caused an increase in foetal resorptions and malformations of the limbs, including polydactyly and syndactyly [15]. In the dog, administration of azathioprine during pregnancy was embryofoetotoxic and teratogenic [16].

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Thioguanine

Lanvis, 2-amino-6-mercaptopurine hemihydrate (MW 176.2)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Thioguanine is a compound similar to 6-mercaptopurine, but more potent than the latter as an inhibitor of growth in various experimental neoplasms. It is incorporated to a significant extent into DNA, and can lower cellular resistance to the effects of ionizing radiation. Thioguanine has been used clinically in cases of leukaemia and also as an immunosuppressant in the treatment of nephrosis and collagen diseases.

The use of thioguanine in pregnancy is contra-indicated, particularly in the first trimester [1,8]. Reference has been made in the literature to treatment, sometimes prolonged, with thioguanine in association with cytarabine, for leukaemia in pregnancy, without side effects in the foetus [9,10].

In laboratory animals, thioguanine was both foetotoxic and teratogenic [2,3,4,6]. In the rat, intraperitoneal doses of 12.5–50 mg/kg on the 11th or 12th day of pregnancy caused an increase in foetal resorptions, cleft palate, and malformations of the tail [4]. Doses of 10 mg/kg on the 7th or 8th days of pregnancy caused 100% resorptions, while administration of thioguanine on the 4th or 5th, or the 11th or 12th days of pregnancy caused nonspecific malformations [6].

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Amethopterin

4-amino-*N*-methyl-pteroylglutamic acid (MW 454.46)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Amethopterin is an antimetabolite of folic acid. Folic acid is a vitamin which provides for transfer of monocarbon units, i.e., insertion into complex molecules of groups containing a single atom of carbon. Folic acid is reduced enzymatically in the organism to tetrahydrofolic acid and analogous compounds, such as folinic acid, which are coenzymes in many essential biosynthetic reactions. These include the synthesis of thymidylic acid and inosinic acid, both yielding components of DNA.

In the absence of folic acid, the synthesis of DNA and RNA is inhibited. Folic acid is activated in the organism by the folic reductase enzyme. Antagonists of folic acid, including amethopterin, form stable combinations with the active site of the enzyme, in such a way that the true substrate, which is folic acid, cannot displace them to any extent. Amethopterin is a potent anti-blastic, used with considerable success in the therapy of chorionepithelioma and hydatiform mole, because of its direct action on chorionic epithelium. It also has a potent abortifacient action because of its marked inhibition of chorionic epithelium.

The use of amethopterin for the treatment of neoplasia in pregnancy, or in failed attempts to produce abortion, is embryofetotoxic and teratogenic [2, 3, 4, 5, 6, 30, 31, 32, 36, 37]. It slows foetal growth and probably causes fundamental cellular changes [6]. The directly damaging effects of amethopterin on placental tissue should be stressed. The drug has been used to inactivate trophoblastic elements in cases of abdominal pregnancy, after extraction of the foetus [33, 34, 35]. Administration of amethopterin at doses of 6–12 mg during the first trimester induced spontaneous abortions in about 84% of cases [1].

In one case, amethopterin was taken at a total dose of 12 mg from the 4th to the 6th week of pregnancy; when abortion took place, the foetus was anencephalic [3]. In another case, the drug was taken at a total dose of 20 mg in the 2nd month of pregnancy. Pregnancy went to term, and the infant had

synostosis of the lambdoid suture, malformations of the occipital bone, and club foot [4]. A pregnant woman took amethopterin during the first trimester at a dose of 12 mg. The neonate had deficiencies in formation of the parietal bone, rudimentary temporal and frontal bones, and synostosis of the hands and feet [5]. Administration of amethopterin during the 3rd month of pregnancy caused spontaneous abortion. The foetus had hydrocephalus, cerebral hypoplasia, cleft palate, and malformations of the extremities [2].

The infant of a mother who had taken amethopterin to procure abortion at a total dose of 12.5 mg during the 2nd month of pregnancy presented with absence of the lambdoid suture, absence of frontal bones, and malformations of the lower limbs [6]. The serious malformations which occurred in cases in which abortion was avoided after taking the drug strongly militate against the use of amethopterin for this purpose.

Despite this, there are references in the literature to the use of amethopterin in pregnancy after the first trimester, both in the treatment of malignant tumours and as an immunosuppressant in severe forms of maternal-foetal Rh immunization, without harmful effects in the offspring [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. Administration of the drug at a dose of 2.5 mg/day from the 5th to the 9th month to a quadripara, severely isoimmunized and with preceding foetal death, was without embryofoetotoxic or teratogenic effects [9]. Administration of amethopterin to 6 isoimmunized patients at various stages of pregnancy had no harmful effects [21]. Similarly, doses of 85–172 mg amethopterin in 4 patients who were isoimmunized, after the first trimester, were innocuous to the foetus [23]. In 3 isoimmunized pregnant women treated with amethopterin at total doses varying from 87.5 to 160 mg after the first trimester, there were no side effects [27]. Administration of the drug at a dose of 2.5 mg/day during the last 10–20 weeks of pregnancy to 6 isoimmunized women had no adverse effects [28]. In 3 patients with carcinoma of the portio after the first trimester of pregnancy, administration of amethopterin at doses varying between 205 and 435 mg had no harmful effects on the offspring [20].

In the rat, mouse, hamster, rabbit, and macaque mulatto, amethopterin was embryofoetotoxic and teratogenic [7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18]. In the rat, intraperitoneal doses of less than 2.5 mg/kg on the 11th or 12th day of pregnancy were foetotoxic [7]. A dose of 1 mg/kg given in a single administration from the 4th to the 8th day was embryotoxic [9]. Doses of 1–3 mg/kg intraperitoneally on the 12th day were embryotoxic [8]. A single administration intraperitoneally of 4 mg/kg on the 17th or 18th day was foetotoxic [8]. A dose of 0.2 mg/kg on the 9th day was embryofoetotoxic [12].

In the mouse, a single administration of 1 mg/kg from the 4th to the 8th day of pregnancy was embryofoetotoxic [11]. In the hamster, a single administration of 1 mg/kg from the 4th to the 8th day of pregnancy was embryotoxic [11]. In the rabbit, a dose of 9.6 mg/kg on the 10th day of pregnancy was foetotoxic and teratogenic [10]. In the macaque mulatto, a single administration

of 3–4 mg/kg from the 18th to the 45th day of pregnancy was embryotoxic and could provoke situs viscerum inversus [12].

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Fluorouracil

Efudix, Fluoro-uracil Roche (MW 130.08)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Fluorouracil is a pyrimidine derivative whose mechanism of action is related to interference with the formation of thymidylic acid, a component of DNA.

One case has been described of reversible poisoning of a foetus after therapy in the last 3 months of pregnancy (total dose 7.5 mg). One and a half hours after birth by Caesarian section, the neonate had cyanosis, tremors, and petechiae. These symptoms regressed after 8 hours of oxygen therapy [1].

In the mouse, rat, and rabbit, fluorouracil was embryofoetotoxic and teratogenic [2,3,4,7,8,9,10]. In the rat, a dose of 25 mg/kg administered from the 9th to the 14th day of pregnancy caused the death of the offspring or the appearance of malformations [2]. At doses of 12–37 mg/kg on the 11th and 12th days of pregnancy, the drug caused anomalies of the central nervous system and the skeleton, and cleft palate [3]. In the rat, mouse, and rabbit, such effects were seen only following treatment in early pregnancy. In later gestation, only a foetotoxic action was observed, with retardation of intra-uterine growth [4].

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Cytarabine hydrochloride

Cytosar, 1- β -D-arabinofuranosyl-cytosine (MW 279.7)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Cytarabine is a pyrimidine nucleotide which contains arabinose in place of ribose, and which acts on the S phase of the cell cycle, blocking the incorporation of pyrimidine into DNA. Phosphorylation is necessary to effect this action. Cytarabine is active in some forms of myeloid leukaemia.

The use of cytarabine in pregnancy is contra-indicated because of possible embryofoetotoxic and teratogenic effects [8,9,10,11]. In one case, the drug was

administered to a pregnant woman from the 5th to the 7th month of pregnancy as an immunosuppressant in maternal-foetal Rh iso-immunization; there were no foetal side effects [12]. Other cases have also been described of treatment with cytarabine in pregnancy without foetal damage [14,15]. A patient with leukaemia was treated from the 26th to the 28th week of pregnancy with 200 mg cytarabine intravenously, together with an oral dose of 160 mg thioguanine, followed by maintenance therapy with reduced doses of the same drugs. There were no harmful effects on the foetus [14,15].

In the rat, mouse, chick embryo, and hamster, cytarabine was foetotoxic and teratogenic [1, 2, 4, 5, 7, 13]. In the rat, a dose of 20–800 mg/kg subcutaneously from the 10th to the 12th day of pregnancy caused foetal resorptions, skeletal malformations of the limbs (polydactyly, phocomelia, oligodactyly), harelip, and malformations of the tail [1]. A dose of 2.5–500 mg/kg from the 9th to the 12th day of pregnancy resulted in foetal mortality at doses upwards of 20 mg/kg. With 100 mg/kg there was arrested development, cleft palate, ectrodactyly, polydactyly, and malformations of the caudal appendix. The teratogenic effects of a dose of 150 mg/kg were antagonized by the administration of 600 mg/kg desoxycytidine on the 12th day of gestation [7].

In the mouse, intravenous doses of 1.5–15 mg/kg from the 7th to the 12th day of pregnancy caused foetal resorptions, arrest of growth, malformations of the digestive tract and limbs, harelip, and deformities of the tail [2]. In the hamster, cytarabine at unspecified doses caused facial alterations with skeletal malformations and cerebellar hypoplasia [4, 5]. In chick embryo, the drug inhibited development when injected into the yolk sac on the 4th day of incubation ($LD_{50} = 0.025$ mg/egg). The surviving embryos showed arrested development on the 18th day of incubation, as well as serious malformations, including absence of the pelvic skeleton, facial coloboma, and corneal cysts [7].

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11.3 Miscellaneous antineoplastic agents

Actinomycin D or dactinomycin

Cosmegen, Lyovac (MW 1255.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Actinomycin D belongs to the actinomycin group, antibiotics produced by various strains of *Streptomyces*. Dactinomycin is the principal product of *Streptomyces parvulus*. As opposed to other species of *Streptomyces*, this microorganism produces dactinomycin in an almost pure state. In general, it is found that the actinomycins exhibit inhibitory effects of varying degrees on Gram-positive bacteria, as well as on some fungi. However, the toxicity of dactinomycin precludes its use in the treatment of infections. Dactinomycin acts mainly by forming complexes with DNA, but not with RNA. Biosynthesis of the latter is inhibited by a secondary route, involving blockage of DNA-dependent RNA polymerase.

Dactinomycin crosses the placental barrier [13]. It is embryotoxic [1] and teratogenic only when administered during organogenesis [2, 3, 13, 17]. However, these effects are less important than would be expected, and in fact two cases have been reported of patients who had taken the drug in the second and third trimesters without adverse consequences to the foetus [4, 12].

In the mouse, rat, rabbit, and chick embryo, dactinomycin was teratogenic [3, 5, 6, 7, 8, 10, 11, 14, 15, 16]. In the mouse, subcutaneous injection of 0.3 mg/kg in a single dose from the 5th to the 12th day of pregnancy was embryofoetotoxic and teratogenic, causing malformations of the nervous system, eye, mouth, tail, and urogenital tract [5]. In the rat, doses of 50–70 μ g/day from the 3rd to the 6th day of pregnancy produced foetal resorptions in 40–50% of cases. From the 6th to the 10th day there were 30% resorptions and 20–50% malformations. After the 10th day of gestation, there was a 10% incidence of foetal mortality but no malformations [6, 7]. A single administration subcutaneously of 0.1–0.3 mg/kg from the 6th to the 11th day of pregnancy was foetotoxic and teratogenic, causing hydrocephaly and malformations of the cardiovascular system and the eye [3], while after the 10th day dactinomycin was not teratogenic [8]. In the rabbit, doses of 150–200 μ g/day from the 8th to the 10th day of pregnancy caused agenesis of the optic nerve, encephalocoele, and spina bifida [10]. In chick embryo, a dose of 0.06 μ g injected after 48 hours incubation gave rise to skeletal malformations [11].

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Mitomycin

6-amino-8- carbamoyl-oxymethyl-1, 1a, 2, 4, 7, 8, 8a, 8b-octahydro-8a-methoxy-5- methylazirino(2', 3': 3, 4)pyrrolo(1, 2a)indolo- 4, 7-dione (MW 334.3)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Mitomycin is an antibiotic with antitlastic activity, inhibiting the synthesis of DNA.

Mitomycin is contra-indicated in pregnancy because of its damaging effects on the foetus (embryofoetotoxic and teratogenic) [1, 2].

In the rat and mouse, mitomycin was embryofoetotoxic and teratogenic [3], and its administration during pregnancy caused damage to the germinal cells of the embryo which was manifested in sexual maturity [4]. In the rat, injections of 2–2.5 mg/kg on the 11th and 12th days of pregnancy were not teratogenic [5]. At doses of 0.05–0.5–1 mg/kg intraperitoneally from the 9th to the 15th day of pregnancy (therapeutic dose 0.04 mg/kg) mitamycin affected the course of the pregnancy only at the highest dose. It also caused malformations and retardation of ossification. Postnatal development was normal, except that there was a high incidence of hydronephrosis encountered at postmortem [6].

In the mouse, injections of 5–10 mg/kg from the 7th to the 13th day of pregnancy were embryofoetotoxic and caused malformations of the central nervous system (anencephaly and spina bifida), the digestive tract (gastroschisis), the eye, the limbs (polydactyly, phocomelia), cleft palate, and deformities of the tail [7]. Intraperitoneal doses of 0.05–0.5 mg/kg from the 7th to the 12th day of pregnancy were teratogenic and inhibited the growth and sexual differentiation of the foetuses [6].

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Bleomycin

(MW ~1400)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Bleomycin is an antineoplastic antibiotic with a depolymerising action on DNA and subsequent blocking of mitosis during the interphase.

The effects of bleomycin on the foetus, the mother, and the pregnancy are controversial. While some authors do not contra-indicate its use [1,2], others advise care, with careful evaluation of the benefits and possible side effects in pregnancy [3,4].

In the rat and mouse, bleomycin was embryofoetotoxic and teratogenic [5]. In the rat, intraperitoneal doses of 0.05–1 mg/kg from the 9th to the 14th day of pregnancy caused inhibition of foetal growth, retardation of sternal ossification, and anomalies of the tail [5]. In the mouse, intraperitoneal doses of 3–5 mg/kg from the 7th to the 12th day of pregnancy caused inhibition of foetal growth, retardation of ossification, and skeletal anomalies [5].

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Daunomycin or daunorubicin hydrochloride

(MW 564.0)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Daunomycin is an antineoplastic antibiotic with a depolymerizing action on DNA in the interphase.

Daunomycin is contra-indicated in pregnancy because of possible adverse effects on the foetus.

In the rat, mouse, and rabbit, daunomycin was embryofoetotoxic and teratogenic [1, 2, 3]. In the rat, injections of 3 mg/kg from the 7th to the 9th day of pregnancy caused foetal resorptions, malformations of the cardiovascular system, the eye, and the urogenital tract [1]. Other authors [2] have not observed any congenital malformations or foetal resorptions at doses of 20 mg/kg from the 5th to the 12th day of gestation [2]. In the mouse, a subcutaneous dose of 1.5 mg/kg from the 1st to the 20th day of pregnancy caused growth retardation [3]. In the rabbit, an intravenous dose of 0.05–0.25 mg/kg from the 1st to the 15th day of gestation caused foetal resorptions but no teratogenic effects [3].

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Adriamycin or doxorubicin

14-hydroxydaunomycin (MW 543.5)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Adriamycin is an antineoplastic antibiotic which exerts its action by blocking mitosis in prophase by inhibition of the synthesis of nucleic acids. It is used in the treatment of carcinoma of the cervix, the endometrium, the ovaries, the lymph nodes, the breast, and the lungs, and sarcomas and osteosarcomas.

Use of adriamycin in pregnancy is contra-indicated because of possible embryofoetotoxic and teratogenic effects [1, 2].

In the rabbit and rat, no teratogenic effects following the use of adriamycin in pregnancy were observed, but there were embryofoetotoxic effects at higher doses [2]. In the rabbit, an intravenous dose of 0.1 mg/kg from the 1st to the 15th day of pregnancy was not teratogenic [2]. In the rat, an intravenous dose of 250 mg/kg from the 1st to the 19th day of pregnancy was without harmful effects [2].

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Vincristine sulphate or VCR

Oncovin (MW 923.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Among the alkaloids of *Vinca rosea* (more than 60), some have oncolytic action. Two of these, vincalucoblastine (VLB) and vincristine (VCR) have been adopted as commercially available drugs. Their structures are very similar, but they differ at the clinical and toxicological levels. There is no cross-resistance, and in fact the two may be used in association. They are used in Hodgkin's disease and in reticulo-, lympho-, rhabdo-myo-sarcoma, in acute leukaemia, in solid tumours of infancy, in neuroblastoma, in mammary and bronchial carcinoma, and in gestochorioepithelioma.

No embryofoetotoxic or teratogenic effects have been reported in the literature. However, some authors advise care in the use of vincristine in pregnancy [1, 2, 3, 11, 12]. We maintain that the use of the drug should be contra-indicated in pregnancy because there are insufficient data available to confirm its safety.

In the rat, mouse, hamster, and macaque mulatto, vincristine was embryo-foetotoxic and teratogenic [4,6,7,8,9,10]. In the rat, intramuscular doses of 0.025–0.075 mg/kg on the 8th day of pregnancy caused an increase in foetal resorption, harelip, and cleft palate [4]. In the mouse, an intraperitoneal dose of 0.25–0.35 mg/kg on the 9th day of pregnancy caused growth retardation, increase in foetal resorption, anencephaly, ocular malformations, and deformities of the limbs and tail [7]. In the hamster, intravenous doses of 0.1–2.6 mg/kg on the 8th day of pregnancy caused foetal resorptions, anencephaly or exencephaly, and ocular malformations [6]. In the rabbit, an intravenous dose (unspecified) on the 7th and 8th days of pregnancy caused ocular malformations [8]. In the macaque mulatto, oral administration of 0.15–0.2 mg/kg from the 27th to the 34th day of pregnancy caused phocomelia and oligodactyly [9]. Oral administration of 0.1–2.3 mg/kg from the 26th to the 28th day of pregnancy caused retardation of growth and increase in foetal resorptions [10].

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Vinblastine or vincalucoblastine sulphate or VLB

Velbe, vinblastine sulphate (MW 909.1)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Vinblastine is an alkaloid of *Vinca rosea* (see vincristine, page 460) which interferes with the metabolism of certain amino acids, particularly glutamic acid, in the incorporation of uridine into RNA, and in mitosis. Vinblastine is effective in the treatment of the lymphomas, chorioepitheliomas, and breast cancer.

Vinblastine does not cross the placental barrier, as evidenced by the fact that it causes leukopenia only in the mother and not in the foetus. It has been used in pregnant women in the first trimester without teratogenic effects

[1,12,13], and some authors therefore consider it safe in therapy of Hodgkin's disease in pregnancy [2,3,11]. Clinical experience confirms the very slight toxicity of vinblastine when administered after the first trimester of pregnancy [4]. However, we believe that the drug should be contra-indicated in pregnancy because there is insufficient evidence from animal experiments of its safety.

In the rat, mouse, hamster, and rabbit, vinblastine administered in pregnancy was embryofoetotoxic and teratogenic [1,6,7,9,10,14]. In the rat, injections of 0.12–0.25 mg from the 7th to the 12th day of pregnancy caused an increase in foetal resorptions, umbilical hernia, gastroschisis, skeletal deformities, and cleft palate [6]. Doses of 0.25 mg on the 9th day of pregnancy caused malformations of the eyes, microcephalus, and spina bifida [7]. In the mouse, subcutaneous doses of 2.5 mg/kg from the 11th to the 14th day of pregnancy caused an increase in foetal resorptions and harelip [9]. In the hamster, intravenous doses of 0.1–2.3 mg/kg on the 8th day of pregnancy caused an increase in foetal resorptions, spina bifida, and ocular malformations [10].

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Procarbazine hydrochloride

Natulan,

p-(*N'*-methylhydrazinomethyl)-*N*-isopropyl-benzamide hydrochloride
(MW 257.8)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Procarbazine is a cytostatic drug of the methylhydrazine group.

Although procarbazine is contra-indicated in pregnancy [1, 2, 3], single cases have been described in which its use was innocuous [4, 6, 10]. In a patient with Hodgkin's disease, procarbazine was administered at doses of 100–150 mg/m² during the first 6 weeks of pregnancy with no embryofoetotoxic or teratogenic effects [4]. In another case, the drug was administered at a dose of 50 mg/day for 20 days from the 12th week of pregnancy without side effects in the foetus [6].

In the rat, mouse, and rabbit, procarbazine was embryofoetotoxic and teratogenic [7, 8, 9]. In the rat, procarbazine administered in a single dose, or in repeated doses of 5–150 mg/kg by injection from the 1st to the 14th day of pregnancy was embryofoetotoxic and caused malformations of the digestive tract (umbilical hernia, gastroschisis), the eye, and deformities of the tail [7]. Oral doses of 5–10 mg/kg from the 8th to the 14th day of gestation caused malformations of the eye and of the limbs [8]. In the mouse, oral administration in a single dose, or in repeated doses of 20 mg/kg from the 8th to the 12th day of gestation, were embryofoetotoxic and caused malformations of the eye and mouth [9]. In the rabbit, oral doses of 200–300 mg/kg on the 14th day of gestation were embryofoetotoxic and caused malformations of the mouth and cutaneous oedema [9].

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Asparaginase or colaspase

L-asparagino-amino-hydrolase (MW ~133 000)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Asparaginase catalyses the hydrolysis of L-asparagine to aspartic acid and ammonia. As a result, it inhibits tumour growth and has been used clinically in the treatment of leukaemia, lymphomas, and melanomas.

Asparaginase is contra-indicated in pregnancy because of possible side effects in the foetus.

In the mouse, rat, rabbit, guinea-pig, and chick embryo, asparaginase was embryofetotoxic and teratogenic [4, 5, 6, 8]. In the mouse, a dose of 20 gamma on the 8th day of pregnancy caused complete resorption of embryos [4]. In the rat, doses of 40 gamma on the 8th day caused resorption of the embryos [4]. At a dose of 500–3000 IU/kg by injection from the 7th to the 13th day of pregnancy, asparaginase was embryofetotoxic and teratogenic, causing exencephaly [5]. In the rabbit, intraperitoneal doses of 150 IU/kg from the 7th to the 16th day of pregnancy were embryofetotoxic, teratogenic, and harmful to the pregnant animal [4]. At a dose of 35 IU/kg intraperitoneally on the 8th day, the drug was embryofetotoxic only [4]. Intravenous doses of 50–100 IU/kg from the 8th to the 9th day of pregnancy were embryofetotoxic and teratogenic, causing malformations of the limbs, digestive tract, tail, and urogenital tract [6]. In the guinea-pig, a dose of 60 gamma/day from the 8th day of gestation caused complete resorption of the embryos [4]. Injected into chick embryos at a dose of 5–10 gamma after 72 hours' incubation, asparaginase caused foetal resorption and retardation of development of the embryos [4].

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Pipobromane

1,4-bis-(3-bromopropionyl)-piperazine (MW 356.09)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Pipobromane is a cytostatic with a mechanism of action analogous to that of the alkylating agents. It is used in the therapy of leukaemia.

Use of pipobromane in pregnancy, particularly in the first trimester, carries considerable risk, because of its embryofetotoxic and teratogenic actions [1, 2, 3].

In the rat and mouse, pipobromane was embryofetotoxic and teratogenic [4]. In the rat, oral doses of 5–30 mg/kg from the 7th to the 10th and from the 11th to the 14th days of pregnancy were embryofetotoxic and caused malformations of the ear, the eyes, the limbs (phocomelia, oligodactyly), the mouth, the cranium, the skin (oedema), and the tail [4]. In the mouse, oral doses of 10–60 mg/kg from the 6th to the 9th and from the 10th to the 13th day of pregnancy were embryofetotoxic and caused malformations of the ear, the eye, the limbs (phocomelia and oligodactyly), the mouth, the cranium, and the tail [4].

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Hydroxycarbamide

hydroxyurea (MW 76.06)

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic	C	C	C		

Contra-indicated in pregnancy.

Hydroxycarbamide is a cytostatic and is rapidly absorbed and eliminated via the kidneys. Its antimitotic action is due to arrest of the biosynthesis of desoxyribnucleic acid. It is used principally in the therapy of chronic myeloid leukaemia.

Hydroxycarbamide is contra-indicated in pregnancy [1], but according to some authors, it may be used with care [2].

In the rat, rabbit, hamster, and macaque mulatto, hydroxycarbamide was embryofetotoxic and teratogenic [3, 4, 5, 6, 7, 8, 11]. In the rat, doses of 185–1000 mg/kg on the 9th, 10th, 11th, or 12th days of pregnancy were teratogenic, causing malformations of the central nervous system, skeleton, and palate [3]. Five hours after administration, 750 mg/kg hydroxycarbamide caused cellular necrosis in the pregnant animals in the limbs, and in the central nervous system of the foetus [4]. Other studies did not demonstrate any chromosome

damage in the embryo after the animal had been treated with 150 mg of the drug on the 13th day of pregnancy was teratogenic [5]. In the rabbit, an intravenous dose on the 11th day of pregnancy was teratogenic [6]. In the hamster, a dose of 50 mg/kg given intravenously from the 9th to the 12th day of pregnancy was foetotoxic and teratogenic, causing exencephaly, spina bifida, and malformations of the cardiovascular system [7]. In the macaque mulatto, a dose of 125–500 mg/kg from the 8th to the 25th day of pregnancy was foetotoxic and teratogenic [8].

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Part 10

Vaccines and sera

	Page
1. Vaccines with dead bacteria or inactivated virus	470
2. Antitoxins	476
3. Vaccines with live or attenuated bacteria or virus	478
4. Immunoglobulins of human origin	484
5. Heterologous immunosera	486

Despite the progress made in the field of antibiotics and chemotherapeutics, the prevention and treatment of many infectious diseases is still based on the use of vaccines and sera, both homologous and heterologous. Vaccination may be carried out with dead or inactivated virus, with live and attenuated virus, or with the corresponding antitoxins. Passive immunity may be conferred by means of hyper-immune fractions of homologus sera (immunoglobulins of human origin) or with heterologous immunosera. A particular aspect is that of prophylaxis by means of isoimmunization against Rh factor with anti-D immunoglobulin. The following vaccines and sera are discussed in this part:

	Recommendation	Page
<i>Vaccines with dead bacteria or inactivated virus</i>		
Cholera vaccine	NC	470
Typhoid and paratyphoid A and B vaccines	C (parenteral) NC (oral)	471
Staphylococcal vaccine	NC	
Antipertussis vaccine	C	471
Colibacillar vaccine	C	472
Antipyogenic vaccine	C	472
Antigonococcal vaccine	C	473
Antirabies vaccine	P	473
Polyvalent anti-influenza vaccine	P	474
Melitensis vaccine	NC	474

Antitoxins

Tetanus antitoxin	NC	476
Diphtheria vaccine	P	476

Vaccines with live or attenuated bacteria or virus

Oral antipolio vaccine	C	478
Anti German measles vaccine	C	478
Antismallpox vaccine	C	480
Anti yellow fever vaccine	C	482
Antituberculosis vaccine	C	482
Antimeasles vaccine	C	483

Immunoglobulins of human origin

Normal human immunoglobulin	NC	484
Antimeasles human immunoglobulin	NC	
Antimumps human immunoglobulin	NC	
Antipertussis human immunoglobulin	NC	
Anti German measles human immunoglobulin	NC	
Antivaccinia immunoglobulin	NC	
Antitetanus human immunoglobulin	NC	
Human anti-D immunoglobulin	P	

Heterologous immunosera

Bubonic gammaglobulin serum	P	486
Anticlostridium immunoserum	P	
Antibotulinus immunoserum	P	
Antidiphtheria immunoserum	P	
Antitetanus immunoserum	P	
Antiophidic immunoserum	P	
Antirabies immunoserum	P	
Anti-anthrax immunoserum	P	

The infectious diseases need to be effectively prevented or combated during pregnancy because they often cause embryofetotoxic effects of an acute or chronic nature. The acute infectious diseases can cause miscarriage, while chronic infections, which are often asymptomatic, are responsible for serious malformations (depending upon gestational age at which they arise) or diseases of the neonate.

Immunoprophylaxis and immunotherapy can cause danger to the offspring. With regard to the problem of vaccination in pregnancy, the general criterion is that those products based on inactive or dead bacteria or antitoxins are not contraindicated, as opposed to those containing live or attenuated strains. However, products of the first kind are also contra-indicated if they cause serious allergic reactions with repercussions on the offspring.

As regards serum prophylaxis in pregnancy, this can be carried out with complete safety using human immunoglobulins, while care is necessary when immunoglobulins derived from animals are used, because of possible anaphylactic reactions. Immunoprophylaxis anti-D during pregnancy should be carried out with care because the safety of this procedure in pregnancy has not been sufficiently evaluated. We do not think that there is sufficient information available to reliably assess the effects of snake vaccines in pregnancy (see page 483).

1. VACCINES WITH DEAD BACTERIA OR INACTIVATED VIRUS

Cholera vaccine

Not contra-indicated in pregnancy.

Cholera vaccine is made up of bacteria killed by heat and formalin.

Vaccination in pregnancy is not contra-indicated, and in fact may be necessary when travelling to countries where cholera is endemic [1, 2, 3, 4, 5, 6, 7, 10, 11, 12].

In the sow, there have been reports of embryofetotoxic effects and teratogenicity as a result of vaccination in pregnancy (cerebellar hypoplasia, hypomyelination, intra-uterine death) [8, 9].

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Typhoid and paratyphoid A and B vaccines

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated parenterally but not orally in pregnancy.

Typhoid and paratyphoid vaccines are prepared from killed salmonella, usually by means of moderate heat.

No reports have been found of embryofetotoxic or teratogenic effects linked to oral administration of typhoid/paratyphoid vaccine [1, 2, 3, 8, 11, 13, 14]. Parenteral vaccination is, however, contra-indicated in pregnancy because of possible local and general reactions, accompanied by hyperthermia, which can cause spontaneous abortion [1, 2, 3, 4, 5, 6, 7, 9, 10, 12].

No experimental studies have been described on the use of typhoid/paratyphoid vaccine in pregnancy in laboratory animals.

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Staphylococcal vaccine

Not contra-indicated in pregnancy.

Staphylococcal vaccine is composed of antigen derivatives obtained from numerous pathogenic strains of *Staphylococcus aureus*.

Vaccination is not contra-indicated in pregnancy, since the vaccine contains substances which function as antitoxins [1], and thus, at most, may create passive immunity in the foetus if they pass across the placental barrier [2].

No experimental studies have been carried out on the use of staphylococcal vaccine in pregnancy in laboratory animals.

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Antipertussis vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antipertussis vaccine is prepared using a suspension of Bordet and Gengou bacilli.

No embryofetotoxic or teratogenic effects have been reported. However, as antipertussis vaccine is administered parenterally, it should be avoided during pregnancy because of severe general reactions accompanied by fever which could cause abortion [1, 2, 3, 4, 5].

No experimental studies have been described on the use of pertussis vaccine in pregnancy in laboratory animals.

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Colibacillar vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Colibacillar vaccine is prepared using numerous killed strains of *Escherichia coli*, *Enterococcus*, *Streptococcus*, *Staphylococcus*, and *Pyocyanea*.

Although there have been no reports of embryofoetotoxic or teratogenic effects linked to vaccination in pregnancy, this should be avoided because of severe general reaction which is accompanied by fever, and can lead to spontaneous abortion [1, 2, 3, 4].

No experimental studies have been described on the use of colibacillar vaccine in pregnancy in laboratory animals.

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Antipyogenic vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antipyogenic vaccine is composed of strains of *Streptococcus*, *Staphylococcus*, *Pneumococcus*, *E. coli*, and *Pyocyanea*, sensitized *in vivo* and killed with ether.

Although there have been no reports of embryofoetotoxic or teratogenic effects linked to vaccination in pregnancy, this should be avoided because of severe general reaction accompanied by fever, which could lead to spontaneous abortion [1].

No experimental studies have been reported on the use of antipyogenic vaccine in pregnancy in laboratory animals.

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Antigonococcal vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antigonococcal vaccine is prepared using numerous strains of *Gonococcus* and *Pseudogonococcus*, together with various strains of *Staphylococcus*, *Streptococcus*, *E. coli*, and *Pyocyanea*.

Although there have been no reports of embryofoetotoxic or teratogenic effects linked to vaccination in pregnancy, this should be avoided because of severe general reaction accompanied by fever, which can lead to spontaneous abortion.

No experimental studies have been reported on the use of antigenococcal vaccine in pregnancy in laboratory animals.

Antirabies vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P	P	P		
Chronic					

To be used with care in pregnancy.

Antirabies vaccine can be prepared from a homogenate of animal nerve tissue, and contains both attenuated live virus and killed virus.

Reports in the literature are unanimous in recommending the use of killed virus only in cases of extreme necessity during pregnancy. Cases of post-vaccinal encephalitis have been described, and there is no agreement regarding the safety of such vaccines for the foetus [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

No experimental studies have been described on the use of antirabies vaccine in pregnancy in laboratory animals.

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Polyvalent anti-influenza vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Anti-influenza vaccine is composed of a mixture of inactivated influenza virus of strains A/Port Chalmers, A/Scotland, and B/Hong Kong.

Although there have been no reports of embryofetotoxic or teratogenic effects linked to vaccination in pregnancy [1, 2, 6, 7], care is advised because treatment with killed virus and chemical antigens introduced parenterally can lead to severe general reactions with fever, and spontaneous abortion [3, 4, 5].

No experimental studies have been described on the use of anti-influenza vaccine in pregnancy in laboratory animals.

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Melitensis vaccine

Not contraindicated in pregnancy.

Melitensis vaccine is composed of antigens derived from strains of various *Brucella* (*Melitemisis*, *Paramelitemisis*, *Abortus*), cultured *in vivo* and killed in ether.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy, and this has been confirmed by the manufacturers [1].

No experimental studies have been described on the use of melitensis vaccine in pregnancy in laboratory animals.

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2. ANTITOXINS

Tetanus antitoxin

Not contra-indicated in pregnancy.

Active immunity against tetanus may be produced in man by administration of antitetanus vaccine, prepared from tetanus antitoxin.

Treatment with antitetanus vaccine may be carried out without danger in pregnancy [1,2,3,4,5,10,11,13,14,15]. In fact, vaccination is recommended in countries with a high incidence of neonatal tetanus [6,8,9,12,16], or when travel is undertaken in countries where tetanus is common [8,9].

No experimental studies have been described on the use of tetanus antitoxin in pregnancy in laboratory animals.

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Diphtheria vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute					
Chronic	P	P	P		

To be used with care in pregnancy.

Diphtheria vaccine is prepared with purified antitoxin.

Although there have been no reports of embryofetotoxic or teratogenic effects linked to vaccination in pregnancy, this should be carried out only when absolutely necessary, because of the danger of hypersensitivity reactions and anaphylaxis [1,2,3,4,5,6,7,8,9,10,11,12].

No experimental studies have been carried out on the use of diphtheria vaccine in pregnancy in laboratory animals.

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3. VACCINES WITH LIVE OR ATTENUATED BACTERIA OR VIRUS

Oral antipolio vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Oral antipolio vaccine is produced from an aqueous suspension of attenuated live poliomyelitis virus, containing three types of virus.

Administration of the vaccine is contra-indicated in the first trimester because it may cause embryofetotoxic effects related to eventual viraemia [1, 2, 3, 5, 6, 7, 8, 9, 20]. Other authors, however, maintain that this vaccine has no embryofetotoxic or teratogenic effects [10, 11, 13, 14, 16, 17, 18].

No experimental studies have been described on the use of antipolio vaccine in pregnancy in laboratory animals.

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AntiGerman measles vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

AntiGerman measles vaccine is composed of the live attenuated virus.

Although occasional references have been made to vaccination carried out accidentally in pregnancy or in patients who have had abortions, and although there were no side effects in these cases [1, 2, 3, 20], it was the unanimous advice of the authors concerned that vaccination against German measles in pregnancy should be avoided [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. When vaccination is necessary in women of childbearing age, contraceptive methods should be used for at least 3 months afterwards.

In 60 women vaccinated during or in the 3 months preceding pregnancy, 14 underwent elective abortion, 3 aborted spontaneously, and 4 gave birth to infants with congenital German measles [11]. Sixty-five women who had been vaccinated in the initial stages of undiagnosed pregnancy underwent elective abortion because of serious danger to the foetus, but this excluded three who miscarried spontaneously [12]. In 343 pregnant women who were vaccinated accidentally in the initial stages of pregnancy, 28 underwent elective abortion. This virus was isolated in the foetal tissues in 21% of cases. However, none of the infants had clinical or pathological signs of congenital German measles [20].

In laboratory animals, the effects of vaccination in pregnancy have not yet been thoroughly investigated, because few animals (among which is the macaque mulatto) respond to the virus [13].

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Antismallpox vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

The vaccine lymph is a liquid obtained from the vesicles caused in calves by cutaneous inoculation with vaccinia virus. The lymph is then diluted with glycerine so as to reduce the number of bacteria to below 5000 ml.

Antismallpox vaccination, like all vaccinations with live virus, is contra-indicated throughout pregnancy because of the well-defined possibility of introduction of congenital vaccinia, abortion, and embryopathies [1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 18, 20, 31, 36, 38, 39, 42, 43]. A pregnant woman who was vaccinated in the 19th week and aborted produced a foetus with generalized vaccinia [5]. Nine neonates have been described with dermopathic vaccinia from mothers vaccinated in pregnancy [15]. A neonate of a mother vaccinated in the 3rd trimester presented with chorioiditis accompanied by destruction of the macula and hypoplasia of the bones [17]. A retrospective study on 17 neonates with generalized eruptions and with umbilicated plaques, who were usually stillborn, showed that the mothers had been vaccinated in the 3rd to 4th months of pregnancy [18].

Other authors maintain that while exposure to the disease may be particularly dangerous to the pregnant woman who has not previously been vaccinated, vaccination, if necessary, was accompanied by only a small risk, especially after the 1st trimester in association with gamma-globulin [2, 6, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 34, 35, 40, 41]. In 4172 pregnant women vaccinated in the 1st trimester, no increase was observed in the number of malformed neonates or perinatal or intra-uterine deaths [25]. In 112 women vaccinated during pregnancy, the frequency of abortions, neonatal deaths, and malformations was not different from that of controls [24]. A study conducted on antismallpox vaccination in New York in 1947, carried out on 5 million inhabitants among whom were many pregnant women, drew the conclusion that vaccination in pregnancy did not increase the number of abortions or malformations over controls [26]. Analysis of about 500 000 vaccinations carried out in Glasgow found only a single case of maternal side effects. A woman in the 3rd month of pregnancy had a vaccinia reaction which was extremely intense and resulted, 11 weeks later, in the birth of a viable infant with typical cutaneous lesions [6].

In the mouse, vaccination in pregnancy was teratogenic in one study [32], although this has yet to be confirmed by others [33].

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Antiyellow fever vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antiyellow fever vaccine is prepared from live virus.

Although there have been no references to embryofetotoxic or teratogenic effects linked to vaccination in pregnancy [7], it should be avoided in pregnancy because of possible viraemia and allergic reactions. Advice to the pregnant woman is unanimously to avoid travelling to countries in which yellow fever is endemic, so that vaccination is not required [1, 2, 3, 4, 5, 6, 7, 8, 9].

No experimental studies have been described on the use of anti-yellow fever vaccine in pregnancy in laboratory animals.

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Antituberculosis vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antituberculosis vaccine is prepared from live organisms, attenuated during their virulent period by physical agents or special culture procedures.

All authors are united regarding the danger of antituberculosis vaccination in pregnancy, because of the possible danger of bacteraemia. Excellent results can be obtained with chemical prophylaxis [1, 2, 3, 4, 5, 6, 7, 8, 9].

No experimental studies have been described on the use of antituberculosis vaccine in pregnancy in laboratory animals.

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Antimeasles vaccine

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	C	C	C		
Chronic					

Contra-indicated in pregnancy.

Antimeasles vaccine is composed of live virus which has been attenuated by passage through chick embryo cells in culture at low temperature.

Although there are no reports of embryofetotoxic or teratogenic effects linked to accidental vaccination in pregnancy, this should be avoided, not only in confirmed pregnancy, but also in cases of possible pregnancy. The manufacturers [1] advise that when a women of childbearing age has been vaccinated, contraception methods should be used at the time.

No experimental studies have been described on the use of anti-measles vaccine in pregnancy in laboratory animals.

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Herpetic vaccine

Antitherpetic vaccine is an extract of a culture of herpetic virus, completely inactivated by irradiation with ultraviolet.

We have been unable to find any information on the use of this vaccine in pregnancy, either in the literature or from the manufacturers. Although no adverse effects have been reported, we believe that antitherpatic vaccine should be contra-indicated in pregnancy and in women of childbearing age who are likely to conceive.

4. IMMUNOGLOBULINS OF HUMAN ORIGIN

Normal human immunoglobulin

Antimeasles human immunoglobulin

Antimumps human immunoglobulin

Antipertussis human immunoglobulin

AntiGerman measles human immunoglobulin

Antivaccinia human immunoglobulin

Antitetanus human immunoglobulin

Not contra-indicated in pregnancy.

These are purified gamma-globulins isolated from human blood. They are used in the prophylaxis and therapy of many diseases of viral origin (hepatitis, varicella, etc.), in order to attenuate possible complications from vaccination (post-vaccinal encephalitis) and in hypo-gammaglobulinaemia.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3], and our clinical experience supports this.

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Human anti-D immunoglobulin

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P	P	P		
Chronic					

To be used with care in pregnancy.

Human anti-D immunoglobulin is prepared from immune human blood and used in the prophylaxis of isoimmunization of Rh factor.

No reports have been found of harmful effects on the human foetus, the mother, or the pregnancy [1, 2, 3]. Forty Rh-negative primigravidae in whom the presence of foetal blood cells was demonstrated in the maternal circulation with a Kleihauer test, were given 100 µg anti-D prophylactically from the 28th to the 32nd week of pregnancy. No side effects were observed in the mother or the foetus [2].

We believe, however, that anti-D immunoglobulin should be used with care in pregnancy, because its mechanism of action indicates that its use be limited

to the period immediately following abortion, premature delivery, or normal parturition. The use of anti-D during pregnancy in order to avoid sensitizing the mother in cases of Rh incompatibility has not been sufficiently studied.

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5. HETEROLOGOUS IMMUNOSERA

Bubonic gammaglobulin serum

Anti clostridium immunoserum

Anti botulinus immunoserum

Anti diphtheria immunoserum

Anti tetanus immunoserum

Anti ophidic immunoserum

Anti rabies immunoserum

Anti anthrax immunoserum

ADMINISTRATION	PREGNANCY Trimester			LABOUR	LACTATION
	1	2	3		
Acute	P	P	P		
Chronic					

To be used with care in pregnancy.

The gammaglobulins are of bovine origin (gammaglobulin bubonic serum) or of antitoxic globulin fractions, (anticlostridium, antibotulinus, antidiphtheria, antitetanus, antiphidic, antirabies, anti-anthrax) purified from the sera of specifically hyperimmunized animals.

Although there have been no references to embryofetotoxic or teratogenic effects linked to the use of heterologous sera in pregnancy [1], such treatment should be carried out with care because of the possible appearance of allergic reactions which may even develop into anaphylactic shock, with severe consequences to the mother and the foetus.

No experimental studies have been carried out on the use of heterologous sera in pregnancy in laboratory animals.

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